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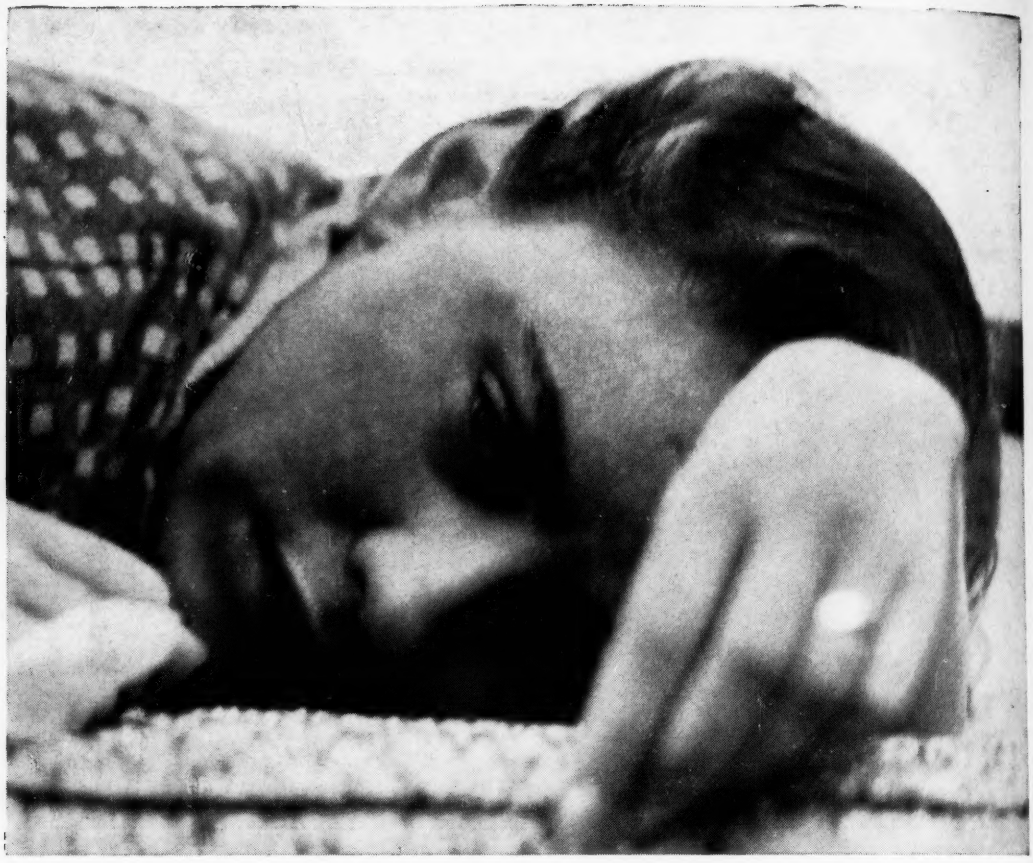

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The Journal of Allergy

VOL. 27 SEPTEMBER, 1956 NO. 5

Original Articles

FOODS, DRUGS, COSMETICS, AND THE ALLERGIST

IRVIN KERLAN, M.D.,* WASHINGTON, D. C.

IT IS a special privilege to meet with you to discuss the health aspects of the Food and Drug Administration activities as they relate to foods, drugs, devices, and cosmetics of particular interest to the allergist.

It is notable that this year marks the fiftieth anniversary of the enactment of Federal legislation dealing with foods and drugs. The Food and Drugs Act of 1906 was the first Federal statute which provided protection of the nation's foods and drugs. Through its provisions, shockingly filthy, fraudulent, and dangerous products were removed from interstate commerce. With the technical advances of science and industry, it followed that this original law failed to encompass the growing needs in dealing with foods and drugs. In 1938 a modernized Federal Food, Drug, and Cosmetic Act was passed. It widened the areas of consumer protection, and for the first time included Federal control of medical devices and cosmetics and additional provisions dealing directly with special dietary foods and new drugs.

The principal responsibility of the Food and Drug Administration is to provide consumer protection through enforcement of the Federal legislation which insures that foods, drugs, devices, and cosmetics are wholesome and unadulterated, safe to use, made under sanitary and controlled conditions, and supplied with honest and informative labeling. Through effective enforcement the public is provided with a confidence in the quality of the regulated products and the manufacturers are protected against unfair competition from inferior or dishonestly labeled goods.

The Food and Drug Administration was one of the first scientific crime-detection agencies, inasmuch as modern technical methods are employed to enforce this law. Potency of drugs and devices and purity of foods would be

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unchallenged without up-to-date methods of scientific analysis to maintain the standards of identity, quality, and strength set forth in the labeling of such articles.

By way of orientation, it may be well to point out that the Food and Drug Administration is a relatively small governmental agency of about 1,000 persons, headed by the Commissioner of Foods and Drugs, with eight technical divisions headquartered in Washington. There are resident inspectional and analytical staffs at district offices in sixteen principal cities. The technical divisions include the Divisions of Antibiotics, Cosmetics, Foods, Medicine, Microbiology, Nutrition, Pharmacology, and Pharmaceutical Chemistry and their professional staffs.

FOODS

The allergist is especially concerned with the composition and production of foods consumed by his patients. In order to be most helpful in advising which foods his patients should avoid, the physician should recognize that all foods are not legally required to declare the names of all the ingredients on their labels. Foods for which there are definitions and standards of identity are not required to designate the names of ingredients on the label. The required ingredients of such foods are named in the official standards. Even so, in certain food standards the regulations do require that optional ingredients be declared. Where there is reason to believe that consumers are interested in a particular ingredient, it is customary to require a legal statement of its presence.

A number of foods do not carry a list of ingredients on their labels because of exemptions from this requirement pending the adoption of definitions and standards of identity for such foods. Exemptions are now in effect for canned fruit and canned vegetables for which standards have not been established as yet; canned clams and canned fish roe; lemon extract, orange extract, and vanilla extract; ice cream, frozen custard, ice milk, sherbets, and water ices; and nonalcoholic carbonated beverages.

For foods for which no definitions and standards of identity have been adopted, the labels must show the common or usual names of each ingredient if it is fabricated from two or more ingredients, except that spices, flavoring, and colorings other than those sold as such may be designated generically without naming each component.

Although food regulations are extensive and detailed, we do not know whether optimal help is being provided to persons suffering from food allergies. As specialists in this field who are closely in touch with the needs of your patients, we would welcome your views in this connection. One of our concerns in this regard currently is whether any appreciable number of persons are sensitive to the minute amounts of certain pesticides found on some foods. From information we have received, it would seem that sensitivity to pesticides is very rare.

DRUGS AND DEVICES

In the Division of Medicine we are most directly concerned with drugs and devices. The public health significance of the safe and effective use of these articles is readily apparent. Foremost of our responsibilities is the detailed review of new-drug applications with respect to the investigative clinical and experimental data dealing with safety of the drugs, as well as the control and methods of their manufacture in order to permit or deny their introduction into interstate commerce. It is a challenging and demanding obligation which requires the highest degree of good medical judgment and awareness. As you readily appreciate, it is one thing to evaluate the investigative results obtained by a few medical experts in carefully selected patients under controlled conditions, but quite another matter to foresee what may arise when the drug is released for nationwide use—and, perhaps, used indiscriminately by some physicians, or by the general public if it is an over-the-counter item. Already more than 10,000 new drugs have been introduced since the new-drug provisions of the Act became effective in 1938.

The Division of Medicine is concerned also with the regulation of all drugs and devices in interstate commerce. We encounter many difficult problems in this connection, some of them involving drugs and devices which are offered to remedy the allergic disease. Too often the products are distributed without sound therapeutic basis. Yet, in order to resort to legal measures to regulate these products, we must be able to prove beyond reasonable doubt in a court of law that the article is misbranded or adulterated. This requires the cooperation of experts who, as a public service, may be willing to use these products in clinical studies in order to demonstrate convincingly their worth as therapeutic agents and to appear in court as expert witnesses.

The nature and frequency of problems in the drug field caused the Administration to seek the expert guidance of allergists in handling some of these problems. In response, a joint committee of the American Academy of Allergy and the American College of Allergists was set up to cooperate with the Food and Drug Administration under the chairmanship of Dr. Leo Criep. This committee has been most helpful through the years. In addition to this special committee, the Academy has several other active committees whose reports and findings are of interest to the Administration. It is hoped that closer liaison may be developed with these groups also so that we may benefit from their deliberations and decisions.

Since the Federal Food, Drug, and Cosmetic Act is designed to inform and protect the user, whether he be the physician or the patient, it is imperative that the labelings of drugs and devices be truthful and carry appropriate contraindications and warnings against misuse. With the rapid introduction of new drugs, it is a major challenge to us to keep abreast of the many untoward and adverse effects associated with the use of drugs. We need to know as quickly as possible all about a drug injury or suspected injury in order to safeguard other users. Too often we do not learn of such experiences until months have passed and the details essential to satisfactory interpretation are

no longer available. This situation led recently to the setting up of a pilot study on "Reporting of Adverse Reactions to Drugs" with the American Association of Medical Record Librarians in cooperation with the American Medical Association, American Society of Hospital Pharmacists, and the pharmacy and drug therapeutics committees of five hospitals to study methodology for selecting, reporting, coding, evaluating, and disseminating such data. This may mark the beginning of an extensive program of reporting of unusual responses to drugs and other products. Your professional practice brings you cases of untoward responses from drugs and cosmetics which would be helpfully revealing if made known to us. Based on a single report, little in the way of control may be feasible, but a series of similar reports would serve to bring about a ready basis for correction of the deficiency. This is especially meaningful in relation to the treatment of patients with a history of an allergic condition, particularly since the physician must balance the hazards involved with the use of his therapy against the extent and nature of the disease under treatment.

COSMETICS

The primary health requirement for cosmetics is that they not be dangerous to users. The cosmetic provisions of the law do not require the listing of ingredients on the label, but if they are listed they must be accurate. As a safeguard to users, patch testing of coal-tar hair dyes is required before application. This practice, unfortunately, is not always observed and major reactions continue to result. The Food and Drug Administration, in investigating all cosmetic injuries reported, has found that an overwhelming proportion develop by reason of allergic reactions. The frequency of reactions seen among users of cosmetics makes it essential for us to learn as much as we can with respect to the offending ingredients so as to protect users from highly sensitizing substances. Your clinical experience and judgment as allergists are fundamental to the resolution of such problems.

From this general review of our activities, it becomes apparent that we share a mutual interest in the protection of your patients' health as well as the public health. With your continued cooperation, we can maintain this trust and fulfill our responsibilities.

SUPPRESSION OF LOCAL ALLERGIC REACTIONS WITH HYDROCORTISONE

ALBERT M. KLIGMAN, M.D., PH.D., AND WILLIAM L. EPSTEIN, M.D.,
PHILADELPHIA, PA.

THE subject of this report is a clinical application of the well-known anti-inflammatory properties of corticosteroids.

In connection with another study, well over 1,000 persons received hyposensitizing intramuscular injections of 3-n-pentadecylcatechol, one of the allergens in dermatitis-producing plants of the genus Rhus. The antigen was administered as a 10 per cent solution in sesame oil, the initial amount ranging from 0.05 to 0.2 c.c.; thereafter, gradually increasing amounts of this solution were given at weekly intervals. On the very first injection, about 15 per cent of the subjects exhibited adverse local reactions consisting of muscle pain, local soreness, swelling, tenderness, redness and, in extreme cases, an acute dermatitis. The changes were principally those of a cellulitis, ranging from a rather circumscribed subcutaneous infiltration or large nodule to an alarming swelling of the extremity into which the injection was made. These reactions generally developed in two to four days, but were sometimes delayed for a week or more. Obviously, it was not possible in such persons to increase the weekly dose in the usual fashion. Only by giving a great many small injections over a long period of time could these persons gradually become tolerant of larger amounts, but most patients deemed this impractical.

To overcome this objection, we hit upon the idea of incorporating corticosteroids into the pentadecylcatechol injection. Hydrocortisone, in particular, seemed attractive, for by now its local anti-inflammatory powers have been well documented. When injected into human skin which is already the site of a chronic dermatosis, psoriasis,[1] or sarcoid,[2] for example, the lesions clear, or when injected along with some skin-testing antigen, such as tuberculin or lepromin, to which the patient is sensitive, the inflammatory reaction which would be expected to ensue is suppressed or reduced.[3] Hydrocortisone is a useful therapeutic agent topically.[4]

It was found that as little as 10 mg. of hydrocortisone drawn up in the same syringe as the pentadecylcatechol prevented or ameliorated adverse local reactions in most persons. The incorporation of 25 mg. gave the most consistent results, which could not be improved by increasing the amount. The preparation used was Cortef acetate (Upjohn), a slowly absorbed, aqueous suspension of hydrocortisone acetate for injection into joints and bursae, 1 c.c. of which

From the Department of Dermatology (Donald M. Pillsbury, M.D., Director), University of Pennsylvania School of Medicine.

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contains 50 mg. of hydrocortisone. The immiscibility of the sesame oil solution of the antigen with the aqueous suspension of hydrocortisone in the syringe is of no account. If a person developed a cellulitis on the first injection of 0.05 c.c., the routine increase to 0.10 c.c. the following week was made, but 25 mg. of hydrocortisone was incorporated; thereafter, this amount was given with each graded weekly injection according to our usual procedure until the maximum weekly dose of 1.5 to 2.0 c.c. was being given. In only a few cases did we have to deviate from the routine schedule because of failure of hydrocortisone to suppress inflammatory reactions sufficiently, and in these the dosage increments were more gradual. It was usually unnecessary to include the hydrocortisone after the patient had received a total of 300 to 400 mg. of pentadecylcatechol, since by then hyposensitization was well under way. There is no contradiction in keeping the dose of 25 mg. of hydrocortisone constant in the face of giving increasing amounts of pentadecylcatechol, for each injection is accompanied by some progress toward hyposensitization; hence, 25 mg. is adequate to cover the larger injections of the antigen because by then the patient has become less sensitive. Of particular interest was the fact that 25 mg. of hydrocortisone suppressed only local reactions at the injection site but not the rashes which sometimes erupted elsewhere in highly sensitive persons. In all, forty-six persons received combined injections of hydrocortisone and catechol. Of these, the suppression of inflammation was sufficiently great in forty-one to permit the routine schedule to be followed. The remaining five experienced definite benefit but of a lower degree, necessitating more gradual increases in the dose. It should be emphasized that in only thirteen of these forty-six cases was there total suppression of inflammation; the more usual response was one of amelioration, permitting the subject to go on with the injections without great discomfort.

We found that 50 to 75 mg. of cortisone daily by mouth maintained over a period of a month or more, adequately suppressed adverse local reactions at the injection site. This was abandoned as too costly and is, of course, not without hazard. It may be noted that corticosteroids in sufficiently high doses are known to suppress antibody synthesis,[5] but no interference with hyposensitization was encountered with the amounts we injected or gave orally. The mechanism of hyposensitization is unknown. Interestingly enough, 25 to 50 mg. of cortisone incorporated in the injections was far inferior to hydrocortisone. This relative impotency is reminiscent of cortisone's lack of anti-inflammatory power when injected into or applied topically on the skin, circumstances in which hydrocortisone is effective.

Benjamin and Cornbleet's[6] demonstration of the anesthetic value of locally injected cortisone and hydrocortisone in suppressing the pain and discomfort attending the injection of substances like thiamine and liver extract is another clinical instance in which local corticosteroids may be useful. Similarly, we found that 5 to 10 mg. of hydrocortisone reduced the painfulness of intramuscular injections of 100 mg. of the tetracycline antibiotics.

Other possible applications of the technique we have used are to prevent local pain and adverse reactions in immunizing injections (typhoid, diphtheria, etc.) and in hyposensitizing atopic patients. Since atopy is a different species of allergy, characterized by immediate rather than the delayed responses of contact dermatitis with which we were dealing, the effects of hydrocortisone may not be comparable.

SUMMARY

In the hyposensitization of patients with allergic contact dermatitis to Rhus plants (poison ivy), the incorporation of 25 mg. of hydrocortisone prevents or ameliorates the occasional adverse local reactions which follow intramuscular injection of the poison ivy allergen.

REFERENCES

1. Goldman, L., Flatt, R., and Baskett, J.: Technic of Assay of an Unknown Steroid for Possible Local Activity in the Skin of Man, J. Invest. Dermat. **23**: 251-257, 1954.
2. Sullivan, R., Mayock, R., Jones, R., and Beerman, H.: Local Injection of Hydrocortisone and Cortisone Into Skin Lesions of Sarcoidosis, J. A. M. A. **152**: 308-310, 1953.
3. Appel, B., Fernandez, J. M. M., and Dougherty, E. F.: The Influence of the Local Injection of Hydrocortone on the Reactions to Tuberculin, Lepromin, Frei and Ducrey Antigens, J. Invest. Dermat. **23**: 237-250, 1954.
4. Sulzberger, M. B., and Witten, V. H.: Hydrocortisone Ointment in Dermatologic Therapy, M. Clin. North America **38**: 321-326, 1954.
5. Dougherty, T. F.: Some Observations on Mechanisms of Corticosteroid Action on Inflammation and Immunologic Processes, Ann. New York Acad. Sc. **56**: 748-756, 1953.
6. Benjamin, F. B., and Cornbleet, T.: Analgesic Effects of Cortisone and Hydrocortisone, Arch. Dermat. & Syph. **69**: 688-693, 1954.

REMOVAL OF RAGWEED POLLEN FROM ENVIRONMENTAL ATMOSPHERE OF PATIENTS

The Evaluation of an Electrostatic Precipitator Combined With an Air Conditioner

Harold S. Novey, M.D.,* John W. Irwin, M.D.,* Jeremy Welts, B.S.,** and Walter S. Burrage, M.D.,*** Boston, Mass.

With the Technical Assistance of Alice Roach, A.B., and Mary Gilchrist, A.B.

INTRODUCTION

THE etiology of ragweed pollinosis and ragweed asthma is known. One method of therapy—separation of the patient from the pollen—will result in complete relief of symptoms. At least tens of thousands, however, still suffer when Ambrosia pollinates. Not all these victims can voyage to mid-ocean or escape to other areas free of the offending agent. Another approach has been the development of devices designed to clear pollen from the air of the patient's room. Beginning with van Leeuwen in 1924,[1] investigators[2-10] have described several types of equipment able to perform with varying success. Some of these authors have stressed technical difficulties and have envisioned more satisfactory clinical results when better machines become available. This article considers an electrostatic precipitator† which has been combined with an air conditioner.‡ This combination represents a logical answer to complaints that air cleaners without air conditioning are unbearable in hot weather.

MATERIALS

The apparatus in Fig. 1 consisted of an electrostatic precipitator† combined into one functional unit with a standard 0.5 horsepower room air conditioner.‡ In electrostatic precipitation,[11] an electrostatic field, intense enough to break down air into free ions, is produced. The positive ions attach themselves to air-

From the Medical Service of the Massachusetts General Hospital and the Department of Medicine, Harvard University.

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†Raytheon Manufacturing Company, Waltham, Massachusetts.

‡Model 51Q2, Carrier Corporation, Syracuse, New York.

borne particles principally by impaction. These charged particles then are drawn into a second, less intense field where they are attracted out of the air stream by the negative electrodes.

In the present model, the ionizer and the collector sections which are required have been integrated into a cell occupying about 0.5 cubic foot. The cell was placed so that it would intercept the recirculated air before it reached the cooling fins of the air cooler. This arrangement allows the air conditioner always to work at peak efficiency by keeping the heat transfer surfaces clean and by preventing condensate from forming on the collector plates and electrically degrading the insulation. The cell can be detached easily and cleaned by rinsing in warm water. With the usual atmospheric dust loading, such cleaning need be done only monthly. The ionizer section consists of fine wires separated

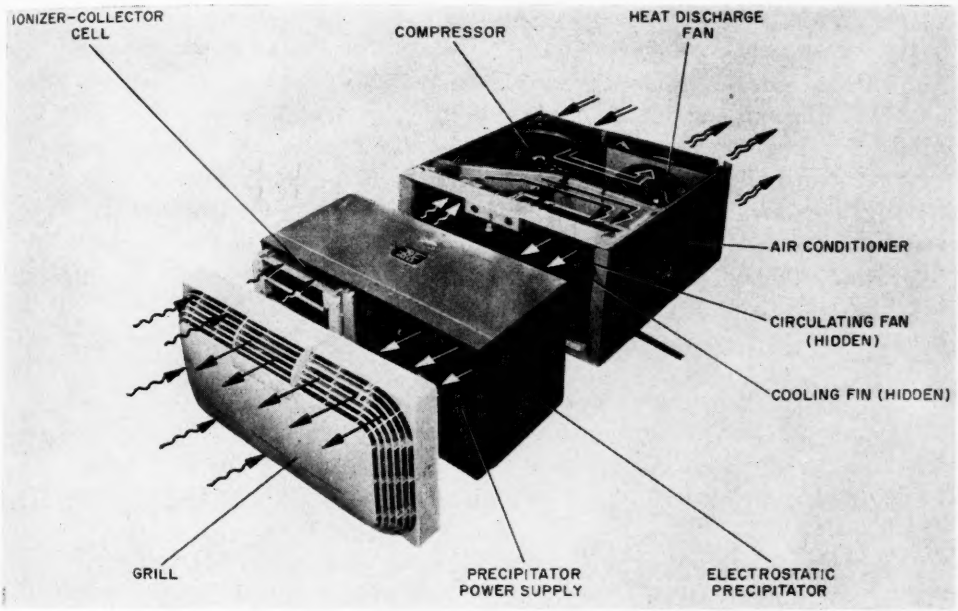

Fig. 1.—Assembly of electrostatic precipitator and air conditioner (exploded view).

equidistantly between large rods. A positive pulsating voltage of 14,000 peak volts is impressed between the wires and the ground rods to produce the intense electrostatic field. Immediately behind the ionizer is the collector section, a series of aluminum plates which are parallel to the air stream. Alternate plates are insulated from each other, and a positive direct potential of 6,000 volts is applied between adjacent plates.

The power for the precipitator is provided by a simple capacitively loaded half-wave rectifier driven from a step-up transformer which supplies 5,500 volts. In action, the collector cell serves as the capacitor in the power supply, while the ionizer acts as the electrical load by being connected across the rectifier. The unusual property of an ionizer—no current will flow unless a

voltage of greater than 8,000 is impressed on it—allows this connection. The voltage impressed on the ionizer is the sum of the capacitor's voltage and the alternating voltage from the secondary of the transformer.

For pollen collection, a standard 3 by 1 inch glass slide was coated by hand as thinly and evenly as possible with a 3:1 mixture of petrolatum and mineral oil. After exposure, the coated side was stained with a solution of 0.8 part 2 per cent aqueous basic fuchsin to one part glycerin, two parts 95 per cent ethanol, and two parts distilled water. Using a microscope (×100 magnification), a competent technician performed all counts by one of three methods: (1) the pollen on the entire slide was identified and recorded (this was the usual way); (2) 1 sq. cm. was studied and the count multiplied by a factor of 18.75 for comparison with an entire slide (outdoor counts); and (3) one transverse microscopic field was examined and the count multiplied by twenty-two fields (this technique was used only for the pollen-saturated slides in the second experiment).

Throughout the pollen season, a daily slide was exposed from noon to noon on a stand similar to that approved by the American Academy of Allergy.[12] This stand was on the roof of a thirteen-story building located within the hospital grounds. In all rooms fitted with precipitators, slides were usually placed at a position which provided for the least disturbance. This was the top of the lower sash of the window containing the unit. Such selection, however, did not represent the ideal place to trap pollen circulating between the patient and the air cleaner.

EXPERIMENTS

These experiments were devised with three purposes in mind: (1) to test the capacity of the apparatus to remove ragweed pollen from the air entering it, (2) to observe its ability to clear a room heavily laden with pollen, and (3) to determine its function under clinical conditions in the hospital, laboratory, and home.

In order to carry out the first aim, 0.2 gram of dry pollen (mixed *Ambrosia trifida* and *Ambrosia artemisiaefolia*) was introduced into the intake section of the precipitator while prepared slides completely covered the outlet. After five minutes the slides were removed, stained, and studied microscopically. A total of twenty-four slides was required to occlude the air exit.

In the second experiment, 1 gram of ragweed pollen was spread over a flat piece of paper (11 by 8½ inches). Simultaneously at opposite ends of the laboratory, as depicted in Fig. 2, 2 grams of pollen was placed directly in front of two nonoscillating electric fans. Each fan had two 11 inch blades. Pollen slides from the six sites were obtained in the following sequence: immediately after the pollen dispersal, after 5, 10, 15, 75, and 165 minutes, and again after 24 hours.

The last group of observations involved patients sensitive to pollen. Those with ragweed asthma severe enough to warrant hospitalization were placed in one of two rooms located in separate hospital buildings. One room was 8 by 8

feet and the other was 12 by 14 feet. These rooms had private toilet facilities, and in each the bed was between the window which contained the precipitator-air conditioner and the door to the corridor. There was only one unit in each room and the windows were nailed down. All patients and hospital personnel involved were requested to cooperate in keeping the doors of the rooms closed. Patients from the Allergy Clinic who were acutely ill with ragweed pollinosis were advised to use the laboratory pictured in Fig. 2 as a possible aid for the

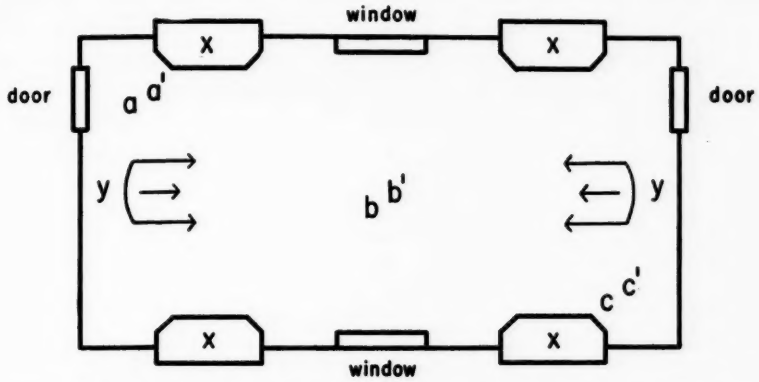

Fig. 2.—Laboratory room. The room contained various pieces of equipment and furniture and measured 28 by 14 by 9 feet, or 3,528 cubic feet. The fans were placed at six-foot heights. The units had the capacity to clear this room of circulating air in about five minutes. *x*, Precipitator-air conditioning unit; *y*, electric fan. *a*, *b*, *c*, Pollen slides, floor level; a^1, b^1, c^1, pollen slides, four feet above.

relief of their symptoms. They were afforded chairs, reading matter, and freedom of the room as they desired. No further information was given. After a tenure in the room, they were examined at various intervals before leaving. Similar units were placed in six homes selected by a local representative of the manufacturer from a list of about fifty patients who were sensitive to ragweed and had not received sufficient relief of symptoms in previous years, despite therapy. Selection was based on suitability of room to the standard unit. Those selected lived in areas as far distant as thirty-four miles. After the units were installed, each patient was visited in order to explain operation of the equipment, and later on to obtain the opinions of each regarding the status of his symptoms and the desirability of the devices.

RESULTS

The first experiment demonstrated that the apparatus did remove all ragweed pollen from the air which entered it. No pollen was found on the slides, even when an estimated 75 million grains were presented to it at one time. The particular unit tested was one of those in the laboratory, and this unit had been in continuous operation, without cleaning, for twenty-five days.

In the second experiment, when the 2 grams of pollen was released into the laboratory, a dense yellow cloud was plainly visible with fingerlike projections advancing on each of the four window units. At the same time, however, some of the yellow particles settled on the floor and furniture, despite the circulating

fans. This deposition resulted in huge collections of pollen on all six exposed slides, as shown in Fig. 3. After five minutes, the counts revealed approximately a 98 per cent decrease, but in the intervals up to 160 minutes, the counts rose to variable heights. Twenty-four hours later, only a few pollen grains were present on four of the six slides (Fig. 3). At least one week, however, was required before the laboratory was completely free of pollen.

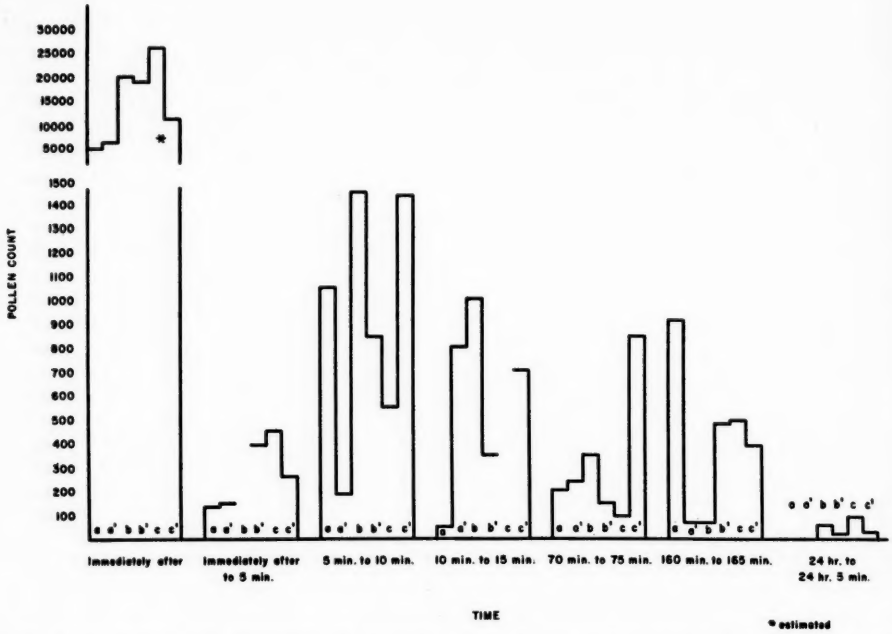

Fig. 3.—Counts after liberation of 2 grams of ragweed pollen into laboratory. Lower-case letters refer to location of pollen slides depicted in Fig. 2.

During this experiment, an unplanned set of observations was secured. Four men were participating in the tests and, by chance, two were patients with proved ragweed pollinosis. Both were asymptomatic before the experiment, for the time was December and New England was covered with snow.

A chronological set of observations was recorded as follows:

10:30 A.M.	2 grams of ragweed pollen dispersed into room.
10:33	J. I.: "Nose itchy," sneezing repeatedly, "head full."
10:35	R. P.: "Head full," "throat itchy."
10:40	J. I.: "Itching in my ears." R. P.: "Eyes itch," sneezing.
10:45	Examination of J. I. revealed moderate palpebral conjunctivitis; nasal turbinates edematous; pallid, clear mucoid discharge.
10:50	Examination of R. P. revealed mild peripheral bulbar conjunctivitis; nasal mucosa as above.
11:10	Both feeling better; less head stuffiness, but R. P. notes itchy throat.
11:30	Both asymptomatic.
2:00 P.M.	2 grams of ragweed pollen again blown into room.

2:03	J. I.: "Itching in eyes and nose."
	R. P.: "Nose stuffed."
2:10	Both sneezing frequently.
2:40	Both asymptomatic.

Throughout this period, the two nonallergic experimenters were free from symptoms.

The clinical studies revealed that none of the patients always obtained complete relief of their symptoms of pollinosis or asthma while in any of the equipped rooms. A few specific examples may serve to illustrate.

A 38-year-old housewife had had severe asthma from mid-August to killing frost since childhood. She had a positive skin test to ragweed. During the ragweed seasons of 1953 and 1954 she required hospitalization and cortisone in early September. She did well throughout the other months of the year. Hyposensitization to ragweed had never been markedly effective. She had experienced persistent asthma from Sept. 7, 1955, until her admission on September 23. She then required intravenous aminophylline and six subcutaneous injections of epinephrine during the first eighteen hours. On September 25 generalized inspiratory and expiratory wheezes were noted in the chest, and the nasal mucosa was boggy, pale, and contained a watery discharge. She gradually became more comfortable and required less medication. At noon on September 29, however, there were inspiratory and expiratory wheezes in all lung fields. Throughout the last six of her seven days of hospitalization, the patient complained frequently of being "cooped up" and "all alone," and the outer door was found ajar on three occasions. These events occurred despite the patient's expressed desire to do anything to get relief from the asthma, even remarking, "I'll go as far away as Arizona." Follow-up examinations of the patient found her asthma-free after November 1. The slides exposed daily in this room yielded a total of one ragweed pollen, but these slides were on top of the air cleaner. Her bed was placed between the door and the air cleaner.

A 48-year-old man who had proved ragweed asthma for ten years was admitted to the other hospital room on August 15 because of severe asthma. During the first twelve hours he received intravenous fluids containing aminophylline and epinephrine. He was comfortable during the next twelve hours, but in the early morning hours of August 17 he was awakened by cough and dyspnea. Generalized inspiratory and expiratory wheezes were found throughout his chest. By August 18 he again required intravenous medication which resulted in improvement, but inspiratory and expiratory wheezes were noted on August 20. Although he was not completely free of symptoms, he was discharged on August 21. At no time did he object to confinement in his room, but on at least two occasions visitors left his door open. No pollen counts were obtained during his hospital stay. During the next week, when the outdoor counts were higher, the slides in this room showed the following counts: 9,0,0,0,3,3, and 5.

Seven clinic patients who had ragweed hay fever, and who had symptoms in spite of hyposensitization, paid a total of eight visits to the laboratory during

the 1955 ragweed season. Four of these visits resulted in definite subjective and objective improvement. For example, one patient noted no itching of his nose or eyes and no tearing after sixty minutes in the room, but he still complained of blocked nasal passages. On examination, the perinasal erythema had subsided, and the watery nasal discharge had cleared. The fastest relief was obtained by another who was "able to breathe again" and showed less edema of the nasal mucosa after thirty minutes. Questionable or no relief was the result of the other four visits. None of the patients were worse.

A study of the pollen counts in Fig. 4 indicates that pollen was found on most of the slides in the homes and, to a lesser degree, on those in the laboratory, but in all cases these were considerably less than the corresponding outdoor counts. Three of the six home patients selected had pure ragweed

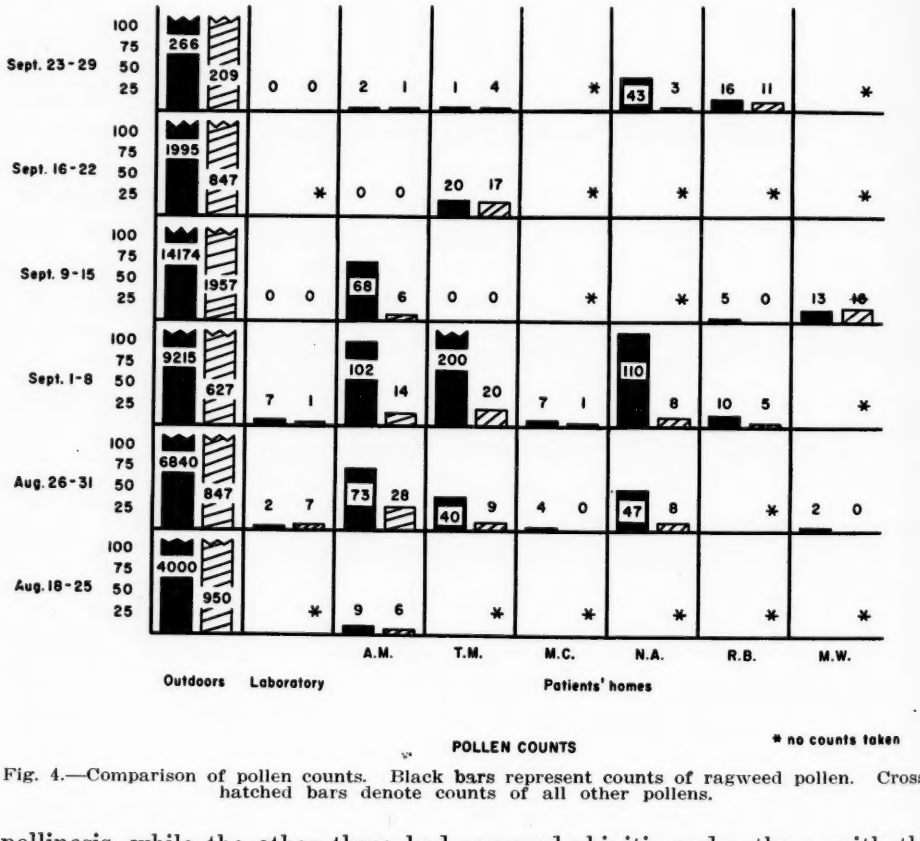

Fig. 4.—Comparison of pollen counts. Black bars represent counts of ragweed pollen. Cross-hatched bars denote counts of all other pollens.

pollinosis, while the other three had ragweed rhinitis and asthma, with the latter the more distressing condition. Patient A. M., whose home had some of the highest counts, had the entrance to the equipped room open during one visit. She had no significant relief of her symptoms of hay fever or asthma and had to be placed on one of the adrenocortical hormones during the last two weeks of the ragweed season. Patient M. C. had less asthma and rhinitis during the nights when she allowed the device to operate and was able to

reduce her bed pillows from three to one. She was not completely free of symptoms and continued her usual medications. During the daytime, the patient usually turned the unit off for fear of overloading the electrical system. M. W., another patient with pollen asthma, began to notice relief after the third night in the room, but he was not completely free of symptoms. He remained in the equipped room mainly at night, but never for a period longer than ten hours. He was careful to keep all exits tightly closed and to change his outer garments before entering the room. His unit was off until one hour before the room was occupied.

All three patients with "hay fever" alone were definitely improved while in the room with the precipitator. The abatement of symptoms in these three usually occurred after one hour in their rooms. N. A. admitted to three or four bad nights, but he considered this a milder season than usual. T. M. believed that he experienced the best season in the past twenty-three years. The third patient usually experienced comfortable nights while sleeping in his room. Shortly after leaving in the morning, his symptoms of rhinitis gradually returned and became very distressing by afternoon.

Initially, most of the patients were disturbed at night by the hum of the compressor, but after two or three nights this noise no longer was distracting. None of the patients otherwise objected to the presence or maintenance of the equipment.

DISCUSSION

The first experiment, in which 0.2 gram of dry pollen (mixed *Ambrosia trifida* and artemisiaefolia) was introduced into the intake section of the precipitator while slides completely covered the outlet, was the most revealing experiment. No pollen appeared on the slides, even though the precipitator had not been cleaned for twenty-five days. Without question, this particular precipitator will remove all ragweed pollen from the air directed to it. This unit also maintained all equipped rooms at a comfortable temperature and humidity. This precipitator-air conditioner, therefore, achieves the objectives of its design.

The full potentiality of the equipment was not realized. If a patient entered a room adequately fitted with this unit before the pollen season and remained there until that pollen season was over, he would doubtless remain completely asymptomatic. This course, however, is even less feasible than the ocean voyage.

Examination of the other experiments raises several questions. When a large quantity of pollen was blown into the laboratory shown in Fig. 2, it was obvious that all the released pollen was not air-borne to the precipitators at once. Quantities of it settled on the floor, counters, books, and articles of furniture. As this deposited pollen was stirred up, it became air-borne. The pollen counts in Fig. 3 add support to this observation. The two experimenters who had ragweed pollinosis are of interest. They promptly developed symptoms when ragweed was released into the laboratory, but they cleared while the ragweed counts were still high. J. I. has severe ragweed pollinosis, where-

as R. P. has only moderate symptoms during ragweed seasons. Yet their experiences during this controlled experiment in December were similar. These observations raise questions which cannot be answered with available data, but they do give rise to speculation.

Obviously, the pollen counts do not determine accurately the quantity of pollen present in a room. In the laboratory experiment there was extreme variability between counts at the same site in the same room. After twenty hours all counts were low, but accumulations of the pollen were seen in several areas of the laboratory for a week. The fact that J. I. and R. P. cleared even though pollen counts were still high might suggest that the air which they breathed did not contain as much pollen as the slide counts suggested.

Study of the patients who visited the laboratory, who were confined to the hospital, and who had units in their bedrooms at home was revealing. None enjoyed confinement in a closed room. They proved this in several ways. It was difficult to entice patients with symptoms of ragweed pollinosis to spend time in the laboratory. Those who came did not remain long, even though some showed marked improvement. Those in the hospital managed to keep their doors to the corridor open. Those with home units usually spent only their sleeping hours in the equipped rooms; several persisted in keeping the doors of those rooms open; and most did not run the units constantly. Even under such conditions, some degree of relief of symptoms was noted by the majority. Since the pollen counts in Fig. 4 often were not high, it might be stated that having doors open was of little importance. All of these units, however, were in windows, and in every instance the patient's bed was between the door and window. The pollen slide was always on top of the precipitator. Obviously, the air with any pollen in it admitted through the door would reach the patient before it did the air cleaner or the pollen slide.

Another point of interest involves the apparent discrepancy between the amount of relief received by those with ragweed pollinosis and by those with ragweed asthma. Again available data are insufficient to explain, and again speculation is in order. The preponderance of inhalants usually will be deposited on the nasal mucosa and eliminated by sneezing or ciliary action, but a demonstrable amount has been found in the lungs, as suggested by the experiments of Scott and associates.[13] An aerosol containing a solution of a radioactive mineral from 0.5 to 1.0 micron in diameter was inhaled and exhaled in one respiration, and it was found that about 2 per cent was immediately exhaled. After seventy-one hours, approximately 32 per cent of the radioactive material had been removed via the bronchial tree, and the remaining 66 per cent presumably remained in the alveolus. When rats were forced to inhale radioactive matter of 1.0 micron or less and the fate of these particles was followed by means of Geiger counters and radioautographs of lung tissue sections, many particles were still present in the alveoli and alveolar ducts after several months. In a series of experiments on dogs, performed over a period of several years, Drinker and Hardenbergh[14] also demonstrated slow elimination from the alveoli. They felt that although bronchiolar absorption

of particles undoubtedly occurs, both because of the surface area available and the anatomic barriers imposed, it was of little importance compared with absorption from the alveoli. By their methods of right lymphatic and thoracic duct cannulation and the simultaneous study of peripheral blood specimens, chemically and immunologically, in living dogs, followed by pathologic section of the lungs, they were able to follow the fate of the following substances introduced into the trachea: dog plasma, purified bovine serum albumin, crystallized egg albumin, hemoglobin, and Pyrex spheres 4.0 micra in diameter. They concluded that even after four hours there was minimal absorption of any of these substances from the alveoli. This was the finding despite production of increased lymphatic drainage from the alveoli by means of increased inspiratory pressure using artificial respiration. These experiments do not explain what happens to inhaled ragweed pollen. It should be pointed out, however, that the alveolar ducts have diameters to 40 micra and that some ragweed pollen in patients with prolonged exposure might reach the alveoli where absorption is slow. Perhaps only the contact of pollen with the nasal mucosa is important in ragweed pollinosis, whereas pollen deeper in the respiratory tree is more slowly absorbed and may play a role in the production of asthmatic symptoms.

SUMMARY AND CONCLUSIONS

1. An electrostatic precipitator, combined with an air conditioner into one functional unit, has been described. This precipitator was designed to remove particles 0.1 micron in diameter from the air presented to the unit.

2. Experiments were performed to determine this air cleaner's ability to remove ragweed pollen from air entering it and to ascertain its competence in clearing pollen introduced into a room. In addition, patients with ragweed pollinosis and ragweed asthma were studied in equipped rooms in the hospital, laboratory, and home.

3. This apparatus removed all ragweed pollen from the air presented to it. Clearing a room into which 2 grams of ragweed pollen was dispersed took more than a week. Much of the pollen settled on the floor, furniture, etc. This equipment does not have the capacity of stirring up every potential particle in the room into the air, but can only remove particles from the air presented to it. The combination with an air conditioner resulted in maintenance of a comfortable temperature in all equipped rooms, even during hot weather.

4. Patients with ragweed "hay fever" usually noted some relief of their symptoms after an hour's occupancy of one of these rooms. Those with asthma due to ragweed did not fare so well.

5. A possible explanation for this discrepancy was discussed, with emphasis being placed on particle elimination from the respiratory tract.

6. This air cleaner, therefore, accomplishes the purposes for which it was designed. Ideally, such equipment should free instantly any room from all particles (even those stuck to items of furniture) and should, in some magic

manner, manage to filter the air free of pollen, even though the patient inhales the air before it is filtered by the precipitator. Such ideal equipment probably will not appear in the near future. In the meantime, this precipitator in combination with an air conditioner will, in a reasonable period of time, free a room of pollen, keep the air of that room relatively free of pollen, and maintain the room at a comfortable temperature in hot weather if the unit is allowed to run and if the doors and windows of the room are kept closed most of the time. The need at present, therefore, is not for a more effective air cleaner, but for more effective use by the human beings in control.

REFERENCES

1. Van Leeuwen, W. S.: Bronchial Asthma in Relation to Climate, Proc. Roy. Soc. Med. **17**: 19-26, 1924.
2. Leopold, S. S., and Leopold, C. S.: Bronchial Asthma and Allied Allergic Disorders; Preliminary Report of a Study Under Controlled Conditions of Environment, Temperature and Humidity, J. A. M. A. **84**: 731-734, 1925.
3. Cohen, M. B.: The Prophylaxis and Treatment of Hay Fever and Asthma in Rooms Made Pollen- and Dust-Free by Means of Mechanical Filters, J. Lab. & Clin. Med. **13**: 59-63, 1927.
4. Peshkin, M. M., and Beck, I.: A New and Simplified Mechanical Air Filter in the Treatment of Hay Fever and Pollen Asthma, J. Lab. & Clin. Med. **15**: 643-649, 1929-1930.
5. Rappaport, B. Z., Nelson, T., and Welker, W. H.: The Effect of Air Filtration on Hay Fever and Pollen Asthma, J. A. M. A. **98**: 1861-1864, 1932.
6. Gay, L. N.: The Treatment of Hay Fever and Pollen Asthma by Air-Conditioned Atmosphere, J. A. M. A. **100**: 1382-1385, 1933.
7. Nelson, L., Rappaport, B. Z., and Welker, W. H.: The Effect of Air Filtration in Hay Fever and Pollen Asthma; Further Studies, J. A. M. A. **100**: 1385-1392, 1933.
8. Vaughn, W. T., and Cooley, L. E.: Air-Conditioning as a Means of Removing Pollen and Other Particulate Matter and of Relieving Pollinosis, J. ALLERGY **5**: 37-44, 1933.
9. Criep, L. H., and Green, M. A.: Air Cleaning as an Aid in the Treatment of Hay Fever and Bronchial Asthma, J. ALLERGY **7**: 120-133, 1936.
10. Friedlaender, S., and Friedlaender, A. S.: Effectiveness of a Portable Electrostatic Precipitator in Elimination of Environmental Allergens and Control of Allergic Symptoms, Ann. Allergy **12**: 419-428, 1954.
11. Westinghouse Electric Corporation: Industrial Electronics Reference Book, New York, 1948, John Wiley & Sons, Inc., chap. 28, "Electrostatic Precipitation."
12. Durham, O. C.: The Volumetric Incidence of Atmospheric Allergens. IV. A Proposed Standard of Gravity, Sampling, Counting, and Volumetric Interpolation of Results, J. ALLERGY **17**: 79-86, 1946.
13. Scott, K. G., Axelrod, D., Crowley, J., and Hamilton, J. G.: Deposition and Fate of Plutonium, Uranium, and Their Fission Products Inhaled as Aerosols by Rats and Man, Arch. Path. **48**: 31-54, 1949.
14. Drinker, C. K., and Hardenbergh, E.: Absorption From the Pulmonary Alveoli, J. Exper. Med. **86**: 7-17, 1947.

AQUA IVY

Toxicity Studies on the Guinea Pig and Treatment of Sensitive Cases

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INTRODUCTION

HYPERSENSITIVENESS to poison ivy develops only after sufficient contact with the leaves or plant parts. Straus[1] reported that 70 per cent of the United States population was sensitive to poison ivy, whereas Heinbecker[2] found no incidence of hypersensitivity among the Eskimos, who never come in contact with it. Deibert[3] found that the American Indians were as susceptible to poison ivy as were the white peoples. Since the American Indian is believed to be closely related to the Eskimos, the difference in incidence of sensitivity to poison ivy was probably due to the great differences in contact with the plant.

Straus[4] reported that feeding the ivy extract alone did not produce cutaneous sensitization, whereas he had previously demonstrated sensitization of newborn infants to poison ivy by means of a cutaneous patch test, or by combined ingestion and cutaneous patch test. He also showed that subcutaneous injection did not produce sensitization; only one of ten infants so treated became sensitized, whereas 73 per cent of forty-eight infants showed sensitization after cutaneous application of an ivy paste.

Ivy leaves or ivy paste applied to nonsensitive persons required ten to twenty-one days for sensitivity to be shown. This was then referred to as a state of hypersensitivity, and it was noted that the incubation period agreed with that found in other types of hypersensitivity. This evidence of an incubation period was first demonstrated by Nestler[5] in 1904 and Low[6] in 1912, and it was confirmed by Field and Sulzberger[7] to be about ten days.

The usefulness of prophylactic therapy for ivy dermatitis by a series of injections or oral doses of ivy derivatives has been reported by many workers. Although the presence of antibodies has not been demonstrated in man and a decrease in skin reactivity has not been noted,* many physicians feel that a refractory state can be produced in patients previously sensitive to contact with Rhus oleoresins and clinically exhibiting dermatitis due to poison ivy or poison oak. The following reports indicate that this can logically be called a

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*After this paper was submitted for publication, Kligman, of the University of Pennsylvania Medical School, reported that hyposensitization occurred after treatment of ivy-sensitive persons with pentadecylcatechol. However, he encountered many severe reactions, which were difficult to control, when dosages sufficient to cause hyposensitization were administered.

process of immunization or hyposensitization, even though the knowledge of the mechanism is lacking. It is in this broad sense that we (and others) use the word *immunity*. For example, Spain and Cooke[8] wrote: "Although the patient received daily oral treatments for the first five months and regular weekly injections for the next eight months, no change whatsoever in the reaction of the skin was apparent; and, since the result clinically was successful, it must be concluded that the degree of immunity developed by treatment cannot be determined by any change in the cutaneous reaction. This condition is, of course, analogous to that found in hay fever."

ORAL ADMINISTRATION

The American Indians chewed the young tender leaves of the poison ivy plant because of its beneficial effect in preventing ivy dermatitis.

Schamberg[9] described successful immunization by oral use of a tincture of *Rhus toxicodendron* in increasing doses.

Spain and Cooke[8] concluded that a satisfactory degree of clinical immunity to ivy poisoning can be developed by the administration in proper amounts of the active principle of Toxicodendron radicans, in the form of either oral treatments or hypodermic injections. They used a milk sugar tablet of the alcoholic extract of ivy for oral administration.

Shelmire[10] employed the ivy oleoresin diluted in corn oil in daily, gradually increasing doses. In taking liquid oral preparations, special care is necessary to avoid irritation of the lips or mouth.

Besser and Urbach[11] obtained very encouraging results with the oral administration of dried seeds of *Rhus toxicodendron* in capsule form.

Gold and Masucci[12, 13] used poison ivy tablets containing from 0.5 to 10 mg. of the poison ivy oleoresin per tablet. Daily treatment with increasing dosages up to 15 tablets of the 10 mg. ivy resin tablet through a total of forty-five days was reported. Seventeen of twenty-five ivy-sensitive patients responded favorably on controlled field exposure. However, 80 per cent of these patients developed toxic reactions during the second and third weeks of treatment. The concentration of oleoresin in their tablets was many times that used by other workers. An excess of the tincture or of oil of *Rhus toxicodendron* taken orally sometimes causes generalized pruritus, dermatitis, gastrointestinal disturbances, or pruritus ani.

Spain and Cooke pointed out that a daily dosage taken over long periods of time was necessary for satisfactory clinical results with oral therapy. It is very difficult for the average patient, unless constantly supervised, to continue his daily schedule of treatment. Therefore, the injection treatment is usually preferable.

PARENTERAL ADMINISTRATION

Spain and Cooke,[8] in 1927, advocated a schedule of treatment using the alcoholic ivy extract where small doses were used in the beginning and gradually increased. They felt that when the dosage was increased too rapidly, or the interval between injections was too short, a constitutional reaction could

occur. Their method developed a satisfactory degree of immunity. The alcoholic ivy was prepared by extracting 10 grams of the dried poison ivy leaves in 100 ml. of absolute alcohol. After extraction overnight, the extract was filtered and sterilized by filtration through a Seitz filter. All glassware and containers must be thoroughly dry, as moisture causes rapid deterioration of the active principle in the alcoholic ivy extract. This concentrated (10 per cent) alcoholic ivy extract is then diluted in absolute alcohol to dilutions of 1:5, 1:50, and 1:500. Immediately before use, this extract must be diluted in a 1 ml. syringe by diluting 0.1 ml. of the 1:500 alcoholic ivy with 0.9 ml. of sterile saline, mixing, and then administering 0.5 ml. subcutaneously. This dilution containing 10 per cent alcohol causes stinging upon injection. The next dosage would be 1.0 ml. of the same mixture, then this procedure is repeated for the 1:50 and 1:5 dilutions of alcoholic ivy.

Biederman[14] observed that 80 per cent of his patients (with positive patch tests and a history of Rhus dermatitis during at least two preceding summers) received complete protection from ivy and oak after treatment with the alcoholic ivy extract described by Spain and Cooke, whereas all untreated control patients developed dermatitis venenata as they had in previous years.

Molitch and Poliakoff,[15] in 1936, immunized forty boys who were proved by patch test to be susceptible to ivy poisoning. The alcoholic ivy extract of Spain and Cooke was administered in weekly injections. None developed dermatitis venenata during the twenty weeks of treatment with normal exposure to poison ivy. These same authors administered one or two prophylactic injections of commercial poison ivy extract in oil to fifty ivy-sensitive boys; seven developed Rhus dermatitis during the season, while the thirty-nine controls who were not immunized developed the dermatitis.

Strickler[16] reported good results with alcoholic ivy extract which he gave at twenty-four-hour intervals for three to five injections as phylactic treatment, followed by oral administration. "Cure" occurred after four injections, sometimes after two. No untoward results were encountered.

Templeton,[17] reporting on five cases with untoward reactions following poison ivy injections, states: "In spite of the few unfavorable cases, I am convinced that the specific antigenic treatment for dermatitis from the Rhus family is of great value. I have had no untoward reactions since I abandoned the larger doses, and my results seem to be equally good."

Clarke and Hanna[18] treated eighty-two boys from 14 to 18 years of age with the alcoholic ivy extract, with satisfactory results. Fifty-six had no poison ivy, nineteen had a rash which was less intense than the previous year, and seven had a rash as bad as or worse than the previous year.

Caulfeild[19] administered the ivy oleoresin in corn oil by intramuscular injection to ivy-sensitive patients in eight to twenty-six injections. He reported satisfactory reduction in quantitative patch tests and an increase in clinical immunity.

Clock[20] used almond oil as the vehicle for carrying the ivy oleoresin, and Keeney[21] advocated peanut oil.

The discussion of toxicity, which appears later in this article, will indicate that the oily ivy preparations have usually been involved where adverse effects were reported.

Strauss and Spain[22] reported good clinical results following treatment with an alum-precipitated pyridine ivy preparation suspended in aqueous solution. This preparation was named Aqua Ivy,* because all previous ivy extracts used either an oil or alcohol as the vehicle in which the oleoresin was dissolved, but this preparation contained the active ivy principles as an alum-precipitate suspended in an aqueous solution.

The Aqua Ivy is prepared by first extracting 10 grams of dried ivy leaves in 100 ml. of pyridine, a weakly basic tertiary amine. After extraction for twenty-four hours, the 10 per cent pyridine-ivy extract is filtered off and Seitz filtered. This pyridine-ivy extract is the stock solution from which the alum-precipitated pyridine-ivy suspension is made. Under sterile conditions, 100 ml. of the 10 per cent pyridine-ivy is mixed with 250 ml. of distilled water and 100 ml. of 2 per cent potassium alum in ¼ N H_2SO_4. The active principle in the pyridine-ivy extract settles out as a dark green, flocculent precipitate. This precipitate is centrifuged down, the supernatant is decanted, and the precipitate is mixed with three separate large washings of sterile saline solution by centrifugation and decantation to remove all excess pyridine and alum. The alum precipitate is then made up to its initial volume of 100 ml. and is thus a 10 per cent (concentrated) alum-precipitated pyridine-ivy suspension; dilutions of 1:5 and 1:50 of this concentrate with sterile saline solution are readily made with this preparation.

The pyridine-ivy alum precipitate, a large molecular oleoresinous compound, is insoluble and stable in water; it is painless upon subcutaneous injection with a tuberculin or allergy type syringe and 26 gauge ¼ inch hypodermic needle.

Strauss and Spain[22] selected a group of twelve ivy-sensitive patients who had responded with poor clinical results to treatment with the alcoholic ivy extract. They were treated the following year with Aqua Ivy, with good clinical results. Sixteen other sensitive persons experienced a season practically free from poison ivy dermatitis following injections of Aqua Ivy.

Gaillard[23] summarized 113 ivy-sensitive patients treated with Aqua Ivy with 77 per cent satisfactory results after one season's treatment and the percentage of good results increased with successive years' treatment. Of forty-six cases treated for two years, 84 per cent had success the second season of treatment. Similar favorable results are being reported by him in more than 300 additional cases.[24] In his report on "The Modern Treatment of Poison Ivy," 78 per cent had satisfactory results after the first season of treatment; 86 per cent had success after the second year of treatment; and 95 per cent had success after the third year of treatment. Gaillard felt that after three years of treatment the immunity might be lasting. Neidorff[25] has treated 318 ivy-sensitive patients with Aqua Ivy, with excellent results.

Loveless[26] patch tested one ivy-sensitive patient before and after an accelerated treatment schedule with Aqua Ivy. Before treatment the patient showed a one plus reaction to 1:100 Aqua Ivy, consisting of one flat vesicle,

*Obtainable at the Allergy Laboratory, University Hospital, 303 East 20th St., New York 3, N. Y., until commercially available.

and after treatment there was "almost nothing" to a patch test with the same dilution of Aqua Ivy and the patient reported being 98 per cent cured.

Fontana[36] treated fifteen ivy-sensitive children with Aqua Ivy, with good clinical results. Most of these patients had been treated previously without success with other ivy preparations.

DISCUSSION OF TOXICITY REPORTS

Some workers have reported on harmful local and generalized reactions following Rhus toxin therapy in patients given treatment orally, or by injection with alcoholic or oily extracts of poison ivy or poison oak. To date, 759 cases in which Aqua Ivy has been used with no untoward local or general reactions have been reported. Shaffer, Burgoon, and Gosman[27] reported, in the *Journal of the American Medical Association,* on a fatal and near-fatal case of acute glomerulonephritis following administration of Rhus toxin administered intramuscularly. Since an intramuscular injection was used, an oily ivy preparation was probably administered, but the authors failed to report the actual preparation used. (Aqua Ivy was not used.) A series of four daily intramuscular Rhus toxin injections was administered to each patient, but there is no indication as to the concentration of the active material in each daily injection. This serves to illustrate the general lack of appreciation of the importance of properly regulated dosages, especially when administered to patients with active dermatitis venenata. These authors extensively reviewed the literature where local and general reactions were noted, but failed to cite numerous reports of beneficial results without toxicity.

Spain and Cooke, in 1927, warned against reactions that occur when large doses are given. Reyer[28] more recently reported upon the flare-up of dermatitis in four patients following treatment with Rhus antigen. It was suggested that Rhus injections were harmful and of no benefit when administered to a patient with dermatitis venenata due to poison ivy. No effort was made to correlate the resultant flare-up with overdosage due (1) to daily intramuscular injections in three cases of from four to eight days' duration and (2) to the concentration of the administered oily ivy preparation.

Rytand and associates[29, 30] reported on the appearance of renal disturbances in seven patients three days to two months after the onset of poison oak contact dermatitis, and only two of these seven patients had received Rhus toxin for the active treatment of their dermatitis. Renal disturbances were therefore shown to occur following the poison oak dermatitis *without* treatment of the dermatitis with a Rhus toxin injection. The question arises as to whether the patients developing the renal disturbances following treatment might not also have done so had no active Rhus toxin been administered, simply as a result of severe poisoning from the direct contact as must have happened in the untreated cases. This also re-emphasizes the need for Rhus toxin in a form such as an aqueous solution which may be easily diluted with saline solution to make higher dilutions of the material readily available when

necessary in the treatment of very sensitive persons or children, and in a slowly absorbed form so that it does not reach the shock organ quickly and in a concentrated dosage.

Howell and associates[31] showed that concentrated poison ivy extract was not nephrotoxic for the rabbit. In fact, they stated: "There is insufficient and inadequate evidence that Rhus dermatitis or extracts administered to ivy sensitive individuals result in systemic injury." They suggested that kidney damage may be caused by a secondary infection, as shown by Callaway and O'Rear.[32]

TOXICITY STUDIES IN THE GUINEA PIG

Toxicity studies with Aqua Ivy on guinea pigs were performed by administering the human prophylactic dosage of Aqua Ivy subcutaneously to twelve normal white guinea pigs, even though the guinea pig weighs only $\frac{1}{300}$ that of an average man.

The human prophylactic series of injections of Aqua Ivy consists of the following dosages:

0.3 ml. of 1:50
0.5 ml. of 1:50
0.7 ml. of 1:50
0.2 ml. of 1:5
0.4 ml. of 1:5
0.6 ml. of 1:5

The last dosage is repeated each four to eight weeks.

The interval between dosages for human beings is one week, but the guinea pigs were given their injections every third day in order to intensify any toxic reactions (should they appear) due to the shorter interval between injections causing greater concentration of the active material in the body during this period.

These guinea pigs injected with Aqua Ivy remained completely normal throughout the test period; they gained weight and their coats remained sleek and luxuriant. It has generally been noted that the coat of sensitized guinea pigs became very sparse and gave a mottled appearance following a dermatitis from a positive contact test. None of the above treated pigs showed any abnormality in their coats.

Another group of fifteen new guinea pigs were treated with ivy by contact on the unbroken epilated skin. The skin was first denuded by cutting the hair with an electric animal hair clipper and the skin was then treated with a cream depilatory* which proved to be nonirritating. Then 0.02 ml. of a 1:10 dilution of pyridine-ivy extract† was deposited on the denuded skin by filling an 0.02

*Nudit, Helena Rubenstein.

†10 Grams of dried leaves, extracted in 100 ml. of pyridine and filtered, gives the concentrated pyridine-ivy extract. The alum-precipitated pyridine ivy suspension (Aqua Ivy) is prepared from this pyridine-ivy stock solution, but the alum-precipitated product is not sufficiently absorbed through the unbroken skin for adequate patch or contact test. Therefore, the stock solution of 10 per cent pyridine-ivy is used for contact sensitization, but dilutions of the 10 per cent pyridine-ivy to make a 1:10 dilution were made in absolute alcohol to prevent any irritating reaction of pyridine itself upon the skin.

ml. pipette to the mark and touching the tip of the pipette to the skin. This minute deposit was allowed to air dry, the tip was touched to the same spot, and the procedure was continued until 0.02 ml. was delivered. In this way, the ivy deposit was confined to a small area and direct contact with the skin was assured. After twenty-four hours, all of the fifteen animals showed an intense inflammatory reaction consisting of vesiculation, redness, and swelling at the site of the patch test. After two or three days, hard, crusty scabs formed which lasted sometimes for weeks. That it was possible to administer 195 times this concentration in Aqua Ivy form by parenteral route to guinea pigs without any signs or symptoms of sensitization, inflammation, or toxicity indicates the safety of this product when administered subcutaneously.

Experiments were planned in order to determine whether the guinea pigs which received the prophylactic series of injections of Aqua Ivy had developed any increased sensitivity to poison ivy. In order to do this, it was first necessary to determine the strongest dilution of poison ivy extract which would just fail to give a positive reaction after contact for twenty-four hours on the denuded skin of normal (new) pigs; a slightly higher concentration of ivy extract giving positive reactions. By titrating out a particular batch of extract in this way, it is possible to show that a particular dilution of ivy extract gives no skin patch reaction in a majority of normal (untreated) pigs. This same dilution was then tested on the series of guinea pigs which had received the prophylactic series of injections and on another group of guinea pigs which previously were actively sensitized to poison ivy.

Preliminary testing showed that 0.02 ml. of a 1:10 dilution of the concentrated (10 per cent) pyridine-ivy gave a marked positive reaction in all of fifteen guinea pigs tested. This patch dosage was therefore a primary irritant and could not be used for any comparative tests. Any other type of ivy extract in sufficient concentration would act similarly. Table I shows that a 1:20 dilution, on the other hand, gave negative patch tests on nine out of twelve new normal pigs when performed in the identical manner. The positive reactions were in no way comparable to the violent reaction of the 1:10 material (described previously); the reactions to the 1:20 dilution of pyridine-ivy consisted of faint pinkness on the patch area and were not followed by crusting or scabs. A 1:50 and a 1:100 dilution of pyridine-ivy gave negative reactions to patch tests in all twelve pigs which had received no other treatment (normals).

When the guinea pigs which had received the human prophylactic series of Aqua Ivy injections were patch tested with 1:20, 1:50, and 1:100 dilutions of pyridine-ivy, exactly similar reactions were noted as with the normal untreated group of pigs. This is clearly seen in the table. There is no evidence of any increased sensitivity following the injection of Aqua Ivy in the complete human dosage administered.

In contrast to these two groups are the results in guinea pigs which were previously sensitized by skin contact with ivy. Ten guinea pigs were sensitized by a single application on the denuded skin of 0.02 ml. of 1:20 pyridine-ivy,

TABLE I. RESULTS OF TOXICITY WITH AQUA IVY IN GUINEA PIGS

ANIMAL NO.	TREATMENT BEFORE PATCH TEST	REACTION TO SKIN PATCH TEST WITH PYRIDINE IVY EXTRACT (0.02 ML.)					
		1:20 DILUTION		1:50 DILUTION		1:100 DILUTION	
		24 HR.	48 HR.	24 HR.	48 HR.	24 HR.	48 HR.
51	None	0	0	0	0	0	0
52	None	0	0	0	0	0	0
53	None	0	0	0	0	0	0
54	None	0	0	0	0	0	0
55	None	+	+	0	0	0	0
56	None	0	0	0	0	0	0
57	None	+	+-	0	0	0	0
58	None	+	+	0	0	0	0
59	None	0	0	0	0	0	0
60	None	0	0	0	0	0	0
61	None	0	0	0	0	0	0
62	None	0	0	0	0	0	0
70	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
71	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
72	Human dosage (Prophylactic) of Aqua Ivy injected*	+	+	0	0	0	0
73	Human dosage (Prophylactic) of Aqua Ivy injected*	+	+	0	0	0	0
74	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
75	Human dosage (Prophylactic) of Aqua Ivy injected*	+-	+	0	0	0	0
76	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
77	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
78	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
79	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
80	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
81	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
82	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
8	Pyridine-Ivy placed on denuded skin†	++	+++	+	++	0	0
9	Pyridine-Ivy placed on denuded skin†	0	++	0	0	0	+
10	Pyridine-Ivy placed on denuded skin†	+++	++++	++	+++	+	0
13	Pyridine-Ivy placed on denuded skin†	+	+++	++	+	0	+-
15	Pyridine-Ivy placed on denuded skin†	0	+	+-	+	0	0
16	Pyridine-Ivy placed on denuded skin†	++	++++	++	+++	0	+-
17	Pyridine-Ivy placed on denuded skin†	+	++	0	++	0	0
19	Pyridine-Ivy placed on denuded skin†	++	+++	+	+++	0	0
21	Pyridine-Ivy placed on denuded skin†	0	+	0	+	0	0
23	Pyridine-Ivy placed on denuded skin†	0	0	0	0	0	0

*Aqua Ivy was injected subcutaneously every third day in the following dosages: of the 1:50 dilution, 0.3 ml., 0.5 ml., and 0.7 ml.; of the 1:5 dilution, 0.2 ml., 0.4 ml., and 0.6 ml.: the last dosage was repeated three times.

†Sensitized by the application of 0.02 ml. of a 1:20 dilution of the 10 per cent pyridine ivy upon the denuded skin and allowing it to remain in situ for four days.

which was allowed to remain in situ for four days. Ten days after the patch had been applied and sensitization had theoretically developed, a hitherto untouched area of the skin was patch tested with the same 1:20, 1:50, and 1:100 pyridine-ivy dilutions as used in the other experimental groups of animals. In marked contrast to the normal or prophylactically treated group of pigs, this sensitized group reacted not only to the 1:20 dilution in most cases, but also to the more dilute 1:50 dilution.

These results are recorded in Table I.

AUTOPSY STUDIES

Six guinea pigs were administered the complete human prophylactic series of Aqua Ivy injections subcutaneously every three days and the top dosage was repeated three times. One week after the last dosage, the guinea pigs were killed and examined macroscopically, and the kidneys were examined microscopically by Dr. A. Hochwald.* The macroscopic examination showed nothing unusual. The microscopic examination showed the usual finding in old guinea pigs of marked congestion in the kidneys. There were no glomerular, vascular, or tubular lesions.

CLINICAL STUDIES

The following patients, reporting for phylactic treatment of existing dermatitis as well as prophylactic courses, were recorded until 101 patients, a number comparable to the Gaillard series, had been summarized as to age, past history, existing dermatitis at time of treatment, dates and amounts of injections, and results. In each case, patients were examined before and after each season to determine the presence or absence of lesions and the extent of severity of lesions following phylactic and prophylactic treatment.

Of the 101 patients studied, ranging in age from 2 to 62 years, it was noted that most commonly those having a history of difficulty were exposed by virtue of living and gardening near newly built suburban homes or by their occupational exposure as gardeners, farmers, and highway and utility maintenance men.

PROPHYLACTIC TREATMENT: METHOD AND RESULTS

In the case of hay fever symptoms, results can be evaluated on the basis of considerable degree of exposure for everyone, even though the pollen crop varies from year to year. With Rhus dermatitis, however, a patient may become cautious after a severe dermatitis. The apparent result of treatment may depend, therefore, not only on the use of immunizing extract, but also on the lessened degree of exposure due to unpleasant past experiences. The cases studied were not ones in which a drastic change of environment, job, or habit was concerned in the results. Spontaneous remissions in some cases cannot be ruled out. The psychotherapeutic effect of a series of injections may conceivably account for some favorable reports in patients regardless of what material is injected; placebo controls were not used. With all these limitations in mind, we

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still consider the use of Aqua Ivy so consistently valuable in clinical practice that we wish to report our results in order to encourage others to further evaluation of the product. Prophylactic treatment series were given 121 times. At the end of the calendar year, each season was recorded as excellent, good, or poor. Each patient either had existing dermatitis typical of the eruption caused by poison ivy or oak, or began treatment because of a history of one or more years of difficulty recurring each year.

An excellent result was taken to be one in which the rest of the year elapsed with less than three or four 12 mm. macules or papules appearing. Larger areas of macules and papules regarded as inconsequential by the patient were considered "good results" unless the area involved was greater than about 3 square inches (20 sq. cm.).

Palm-sized or larger areas, vesiculation of any area, or failure of the injection to help, in the opinion of the patient, automatically placed the series in the "poor result" category.

Using these rough criteria, the results were as follows:

Prophylactic Result	*Courses*	*Per Cent*
Excellent	63	52
Good	50	41
Poor	8	7
Total	121	100

Patch tests were not done, as it was not considered necessary to determine closely the degree of sensitivity.

ILLUSTRATIVE CASE HISTORIES

CASE 1.—R. A., 5 years old, reported with a history of having been seen by a family doctor every summer for three years for a rash on the arms, hands, and exposed areas of the lower legs, considered typical of poison ivy dermatitis. Aqua Ivy dosage used at seven- to fourteen-day intervals, beginning in April, was:

April 26	0.2 ml. of 1:50
May 15	0.5 ml. of 1:50
May 22	0.7 ml. of 1:50
May 29	0.1 ml. of 1:5
June 12	0.5 ml. of 1:5
July 3	1.0 ml. of 1:5
August 2	1.0 ml. of 1:5
August 24	1.0 ml. of 1:5

A few papules, not related to the injection, were noticed during August, but the patient's mother felt that this was a great improvement over the prior years with similar opportunity for exposure. This was considered a good result.

CASE 2.—A. C., a 34-year-old salesman, gave a history of a vesicular rash on the forearms each summer for ten years, attributed to week-end exposure in gardening and at picnics. He required several days of hospitalization for the first three summers. Due to lack of exposure to poison ivy, he had slight or no difficulty for two years. This interval was

followed by increasingly troublesome ivy dermatitis of the forearms every summer during the next five years. He came in for treatment and was given the following limited series of Aqua Ivy injections:

June 20	0.3 ml. of 1:50
June 22	0.5 ml. of 1:50
June 24	0.7 ml. of 1:50
June 28	0.1 ml. of 1:5

He had a satisfactory result which lasted all summer, even though his exposure was essentially unchanged.

CASE 3.—A. C., a 62-year-old salesman with profuse ivy growth in his suburban gardening area, suffered a repeated maculopapular rash with intense itching on the wrists and forearms each summer for four years. Week-end outdoor work was usually followed by an eruption. The diagnosis of ivy poisoning was confirmed by two physicians. The initial series of Aqua Ivy injections was given at the same time that pollen extract was administered and the intervals were therefore longer than usual. The dosage was as follows:

May 28	0.3 ml. of 1:50
June 18	0.5 ml. of 1:50
July 2	0.7 ml. of 1:50
August 2	0.2 ml. of 1:5

From October, 1951, through December, 1954, a 0.7 ml. dose of 1:5 dilution of the alum-precipitated pyridine extract was given monthly through the summer and a 0.5 ml. dose was given each month through the winter. Although the exposure remained the same, or even increased as the patient felt free to do more work in the garden, absolutely no lesions appeared and his four years of treatment were rated "excellent."

CASE 4.—L. A., 8 years old, had a history of dermatitis venenata each summer since the age of 3 years. Her Aqua Ivy doses were:

April 22	0.3 ml. of 1:50
April 28	0.7 ml. of 1:50
May 6	0.2 ml. of 1:5
May 20	0.4 ml. of 1:5

This patient remained free of dermatitis, in the suburban environment in which the dermatitis usually occurred, until about August 1, when her usual maculopapular eruption of the hands and face developed. The mother had not understood the need for booster doses and relied on the initial series, which also fell short of the 0.7 ml. we had intended to reach before a four-week booster interval. This result was recorded as "poor," and the eight-week interval of control, followed by recurrence, can be interpreted as supporting our feeling that booster doses of 0.5 to 0.7 ml. of 1:5 Aqua Ivy should be maintained every four to six weeks for best results.

PHYLACTIC USE OF AQUA IVY: DISCUSSION AND RESULTS

Eighty-five patients appearing with poison ivy dermatitis were treated with Aqua Ivy. Mild dermatitis responds well to topical applications and antihistamines, and may not require further treatment of any kind. In more protracted or more disturbing cases, phylactic injections at two- to four-day intervals of minute doses of Aqua Ivy may alleviate the discomfort and shorten the period of attack. In the more severe or extensive attacks of dermatitis venenata, where exacerbations of symptoms may follow injection therapy, the steroid hormones have proved especially helpful. This is due to the self-

limited character of the condition, which consequently does not demand protracted treatment.[33] These hormones do not permanently alter the original hypersensitivity to the Rhus toxin. It is recognized that the hormones act by suppressing the inflammatory reaction rather than by affecting the immune mechanism. This is observed when premature discontinuance of the hormone is followed by reappearance of the rash. The evaluation of steroid therapy for the relatively minor ailment, such as ivy dermatitis, hinges upon further knowledge about the degree of adrenal suppression found with even a few doses of cortisone. Severe infection or surgery has been reported to precipitate shock and even result in death. The advisability of treatment of relatively mild ivy dermatitis with such a potent hormone is therefore questionable.

Topical application of hydrocortisone not only has been disappointing, but at times it seems to be responsible for the spread of the rash beyond its original limits; this is thought at times to be due to the oily nature of the vehicle in which it is sometimes dispensed. A recent confirmation of this was by Eskind and associates,[34] who found no significant difference in seventy-seven patients treated by topical hydrocortisone in various vehicles and fifteen given placebo therapy. Exceptions were four patients relieved where angioedema, rather than vesiculation and erythema, was the primary complaint.

Average phylactic treatment for adults with mild to moderate cases of dermatitis venenata consisted of subcutaneous injections every two to four days as follows:

Dosage: No. 1 0.1 ml. of 1:50 Aqua Ivy
No. 2 0.2 ml. of 1:50 Aqua Ivy
No. 3 0.3 ml. of 1:50 Aqua Ivy

In a few severe cases, the initial dosage was repeated or the interval lengthened to avoid overdosage. The dermatitis usually dries up by the second or third injection and the patient reports general improvement.

Phylactic treatment is no longer necessary for general use since the advent of corticosteroids, but it is reported here to substantiate the safety of Aqua Ivy and its usefulness even during active dermatitis venenata. Local applications varied according to the degree of oozing and vesiculation. These varied from wet dressings with potassium permanganate 1:20,000 in severe cases to antipruritic agents for milder maculopapular stages. We feel that the application of ointments and creams early in the dermatitis is often responsible for mechanically spreading the poison ivy oleoresin to adjacent skin.

Among the 101 patients studied, there were eighty-five times when a series of one to four injections was given for ivy dermatitis present at the time of the initial visit. The need to withhold ivy injections exists chiefly in the acute vesiculation or oozing of relatively large areas from intimate exposure to ivy leaf or vine, or in cases where there have been several full doses of ivy in oil during the preceding ten days. There have been many warnings in reference to such radical treatment with injections of ivy in oil, and we heartily endorse caution.

In this series, the results were as follows:

Phylactic Results	*Courses*	*Per Cent*
Excellent	42	49
Good	37	43
Poor	6	8
Total	85	100

DISCUSSION

Aqua Ivy, being alum precipitated, is very slowly absorbed so that larger dosages are administered both as an initial dose and as a final concentration in the prophylactic immunization series. This slower absorption and high dosage level, which is greater than that obtainable with the alcoholic or oily ivy preparations, probably explains, in part, (1) the freedom from toxic reactions and (2) the more successful clinical results seen with this Aqua Ivy preparation. Aqua Ivy, being in the body for a longer period of time and in greater concentration than has heretofore been possible with other preparations, gives the body defenses a greater opportunity to develop immunity. Coulson and Stevens[35] showed that ovalbumin which was alum precipitated had a sensitizing capacity in guinea pigs from four to nearly 400 times greater than that of ovalbumin in saline solution, depending upon the route of administration. Exacerbation of the dermatitis is rare with this preparation (in spite of the higher initial and final dosages to known sensitive persons) because of the nature of this new pyridine-oleoresin compound and its slow absorption. The maximum doses of the alum-precipitated, pyridine-ivy extract can be given at much longer (eight-week) intervals with very little fear of any type of untoward reaction, such as may occur at times with the usual ivy extracts.

SUMMARY

1. Guinea pigs who received the full human dosage of Aqua Ivy subcutaneously were not made more skin-sensitive to poison ivy, as demonstrated with quantitative serial dilutions by contact test.

2. Nephritis, even when large dosages of Aqua Ivy were administered, was not found on autopsy in guinea pigs.

3. A group of 121 prophylactic series of Aqua Ivy injections were administered, with 93 per cent excellent or good results.

4. There was no incidence of nephritis or exacerbation of dermatitis in this series, even when Aqua Ivy was administered to children as young as 2 years of age.

5. Observations on the phylactic use of Aqua Ivy in mild to moderate ivy dermatitis are included only to emphasize the lack of exacerbations (with good clinical results) following its use as described. Current therapy of choice is systemic hydrocortisone for the acute severe case and Aqua Ivy for subsequent prophylaxis.

REFERENCES

1. Straus, H. W.: Artificial Sensitization of Infants to Poison Ivy, J. ALLERGY **2**: 137, 1930.

2. Heinbecker, P.: Studies in Hypersensitiveness; the Susceptibility of Eskimos to an Extract From Toxicodendron Radicans (L), J. Immunol. **15**: 365, 1928.
3. Deibert, O., Menger, E. F., and Wigglesworth, A. M.: Studies in Specific Hypersensitiveness; Relative Susceptibility of the American Indian Race and the White Race to Poison Ivy, J. Immunol. **8**: 287, 1923.
4. Straus, H. W.: Experimental Study of the Etiology of Dermatitis Venenata, J. ALLERGY **5**: 568, 1934.
5. Nestler: Quoted by Low.[6]
6. Low, R. C.: Anaphylaxis and Sensitization, New York, 1925, William Wood & Company.
7. Field, H., and Sulzberger, M. B.: Experiments in Poison Ivy Sensitivity, J. ALLERGY **7**: 139, 1936.
8. Spain, W. C., and Cooke, R. A.: Studies in Hypersensitiveness. XXVII. Dermatitis Venenata: Observations Upon the Use of a Modified Extract From Toxicodendron Radicans, J. Immunol. **13**: 93, 1927.
9. Schamberg, J. F.: Desensitization of Persons Against Poison Ivy, J. A. M. A. 73: 1213, 1919.
10. Shelmire, B.: The Poison Ivy Plant and Its Oleoresin, J. Invest. Dermat. **4**: 337, 1941.
11. Besser, J. P., and Urbach, J.: Peroral Prophylaxis of Poison Ivy. Dermatitis, Ann. Allergy **10**: 169, 1952.
12. Gold, H., and Masucci, P.: Oral Prophylaxis Against Poison Ivy, J. ALLERGY **13**: 606, 1941-42.
13. Gold, H., and Masucci, P.: Prophylactic Oral Therapy Against Poison Ivy, J. ALLERGY **13**: 157, 1941-42.
14. Biederman, J. B.: Observations on the Relation of Poison Ivy and Poison Oak, New Eng. J. Med. **219**: 117, 1938.
15. Molitch, M., and Poliakoff, S.: Prevention of Dermatitis Venenata Due to Poison Ivy in Children, Arch. Dermat. & Syph. **33**: 725, 1936.
16. Strickler, A.: The Toxin Treatment of Dermatitis Venenata, J. A. M. A. **77**: 910, 1921.
17. Templeton, H. J.: Untoward Reactions Following Toxin Treatment for Dermatitis Venenata, Arch. Dermat. & Syph. **20**: 83, 1929.
18. Clarke, J. R., and Hanna, C. M.: The Treatment of Rhus Poisoning by Alcoholic Extracts in a Small Group Controlled by Preliminary Patch Tests, J. ALLERGY **13**: 599, 1942.
19. Caulfeild, A. H. W.: Prevention of Poison Ivy Dermatitis by the Intramuscular Injection of "Rholigen," Canad. M. A. J. **37**: 18, 1937.
20. Clock, R. O.: Rhus Dermatitis: Its Treatment With Poison Ivy Extract, M. J. & Record **122**: 93, 1925.
21. Keeney, E. L., Sunday, S., Gay, L. N., and Lynch, K.: Poison Ivy Dermatitis; the Diagnostic Value of the Patch Test Made With an Ether Extract From Fresh Leaves and Stems of the Poison Ivy Plant, Bull. Johns Hopkins Hosp. **69**: 482, 1941.
22. Strauss, M. B., and Spain, W. C.: Studies on Poison Ivy and Other Dermatitis Producing Plant Parts Wherein Active, Resinous Principles Are Suspended in Aqueous Solution, J. ALLERGY **17**: 1, 1946.
23. Gaillard, G. E.: Poison Ivy: A Summary of One Hundred Cases Treated With Aqueous (Alum Precipitated Pyridine) Extract, J. ALLERGY **21**: 55, 1950.
24. Gaillard, G. E.: Fundamentals of Modern Allergy; The Modern Treatment of Poison Ivy, New York State J. Med. **56**: 2255, 1956.
25. Neidorff, H. A., Altoona, Pa.: Personal Communication.
26. Loveless, M. H., New York, N. Y.: Personal Communication.
27. Shaffer, B., Burgoon, C. F., and Gosman, J. H.: Acute Glomerulonephritis Following Administration of Rhus Toxin, J. A. M. A. **146**: 1570, 1951.
28. Reyer, W. A.: Exacerbation of Ivy Dermatitis by Rhus Antigen Injections, Ann. Allergy **11**: 91, 1953.
29. Rytand, D. A.: Fatal Anuria, the Nephrotic Syndrome and Glomerular Nephritis as Sequels of Dermatitis of Poison Oak, Am. J. Med. **5**: 548, 1948.
30. Rytand, D. A., Burna, D. W., and Cox, A. M.: Periarteritis Nodosa Following the Dermatitis of Poison Oak and of Primrose, Stanford Med. Bull. **6**: 319, 1948.
31. Howell, J. B., Goth, A., and Fashena, G. J.: Rhus Toxicodendron—Possibility of Systemic Effects, A. M. A. Arch. Dermat. & Syph. **70**: 426, 1954.
32. Callaway, J. L., and O'Rear, H. B.: Pyogenic Infections of Skin—Etiologic Factor in Acute Glomerulonephritis of Children, A. M. A. Arch. Dermat. & Syph. **64**: 159, 1951.

33. Ekblad, G. H.: The Use of Corticotrophin (ACTH) and Cortisone in Urticaria and Dermatitis, U. S. Armed Forces M. J. **3**: 839, 1953.

34. Eskind, I. B., Sigafoos, R. B., and Kelso, R. W., Jr.: Treatment of Rhus Dermatitis With Topical Hydrocortisone; a Clinical Evaluation, Arch. Dermat. & Syph. **69**: 410, 1954.

35. Coulson, E. J., and Stevens, H.: Quantitative Studies in Anaphylaxis. III. Effect of the Alum Adjuvant and Route of Administration on the Sensitizing Dose, J. Immunol. **61**: 119, 1949.

36. Fontana, V. J.: Eczematous Dermatitis in Children, GP **10**: 47, 1954.

DIARRHEA CAUSED BY FOOD ALLERGY

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FOOD allergy as a cause of colic and diarrhea, with or without other gastrointestinal symptoms, in infants and young children has long been recorded by Talbot,[28] Shannon,[27] Laroche, Richet, and Saint-Girons,[10] Schloss,[26] Ratner,[13] Greer,[7] Rowe,[14, 15] Vaughan and Black,[29] and others. Rubin,[25] in 1940, reported loose stools with traces of blood, small clots, and mucus, along with colic, three weeks after starting canned cow's milk; this was relieved in forty-eight hours by the elimination of milk. Clein,[3] in 1951, stressed diarrhea along with other allergic manifestations due to milk allergy. Most recently, in 1955, Collins-Williams[4] reported diarrhea, vomiting, and severe shock from forced ingestion of evaporated milk. Fewer discussions have been published regarding this condition in adults. Andresen,[1] since 1923, has reported uncomplicated diarrhea along with that in chronic ulcerative colitis due to food allergy in adults. Eyermann, in 1927, studied five cases of allergic diarrhea along with other gastrointestinal symptoms arising from allergy. One of us (A. H. R.),[14, 15] in books published in 1930 and 1936, reported cases of this diarrhea and its occurrence in 15 per cent of 150 cases of gastrointestinal allergy. One man with diarrhea due to milk had taken one teaspoonful of milk as a laxative for a number of years. In another, a few drops of milk produced five to fifteen watery movements in two to three hours. Piness and Miller[12] recorded diarrhea, incontinence, melena, emaciation, and chronic invalidism due to food allergy in one patient who previously had had a cecostomy for possible relief. Friedenwald and Morrison[6] reported allergic diarrhea in adults. In one woman the diarrhea had continued steadily for six months. All studies had been negative except for achylia. Hydrochloric acid was ineffectual. Milk allergy was the sole cause. Browning[2] also found diarrhea arising from food allergy. Alvarez emphasized milk allergy as being responsible for diarrhea and other abdominal symptoms in 20 per cent of 500 cases. Cardon, in 1944, wrote an interesting report on five adults with diarrhea, cramping, abdominal soreness, and tenesmus due to milk allergy. Spastic colons were seen by x-ray in some cases. Literature on allergy to cow's milk, and especially on resultant shock and even death therefrom, is reviewed.

Milk allergy, thus, is by far the most frequent cause of allergic diarrhea. Although most reports deal with the condition in infants and children, this article will stress allergic diarrhea due to foods in adults, even after the age of 50 years. Thus, all physicians (especially internists, gastroenterologists, and

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pediatricians) must keep it in mind. Moreover, our experience indicates that allergy to milk is more common than to any other food as a cause of the many manifestations of food allergy. Reviews of the literature on milk allergy, with special discussion of many interesting cases and observations, including those of the senior writer, were included in his books[14, 15] published in the 1930's.

This is a study of twenty-six adults and four children relieved of chronic, troublesome diarrhea by the elimination of certain foods. The frequency of such diarrhea is indicated by its occurrence in approximately 220 patients with probable gastrointestinal allergy studied in the last seven years. No cases of chronic ulcerative colitis or regional enteritis, usually due in our opinion to food allergy[19, 23] and at times to pollen allergy,[24] were included in this group.

The ages of onset and at our first conference are shown in Table I. Diarrhea had continued for an average of 7.7 years. The infrequency of infants and children in this series is due to the small number of children referred by pediatricians because of diarrhea. The number of patients past the age of 40 years and of female patients is noteworthy.

TABLE I

AGE (YEARS)	NUMBER OF CASES
Age at Onset	
0-6	5 (4, 4, 6 and 12 months, 6 years)
20-40	9
40-50	10
50-60	6
Age When First Seen by Writers	
0-5	4
20-40	7
40-50	7
50 up	12

NUMBER OF WATERY OR SOFT STOOLS IN 24 HOURS	
NUMBER OF STOOLS	NUMBER OF CASES
1-3	4
3-6	12
6-10	10
10 up	4
Duration of diarrhea	7.7 years (¼ to 50 years)
Intermittent relief	16 cases
Cramping (abdominal)	20 cases
Constipation (intermittent)	6 cases
Constipation with mucus	4 cases (2 severe)

That the diarrhea was definite or severe is shown by the fact that no patient had less than three stools and most had three to ten stools a day (Table I). During severe attacks, some passed up to twenty stools. Stools were usually liquid and at times mushy, associated with urgency and varying amounts of bloating, gas, and tenesmus. In a few cases, incontinence occurred, keeping patients at home or in proximity to a rest room. The anal canal at times was raw and tender. Diarrhea occurred for one to four days every one to three weeks or only when known allergenic foods were taken, or in some cases continuously for weeks or longer periods. Cramping in different parts or in all of the abdomen varied in degree and frequency. In some cases, it doubled the patient up for minutes or longer periods. In one child, crying continued throughout the night, associated with weakness and sweating. The diarrhea occurred often on arising or for one to three hours after breakfast or it developed after meals or through the afternoon. In one patient it never occurred at night. Intermittent constipation and diarrhea occurred in six

patients. In four of these, mucus was present, being marked in two cases. As in many cases of mucous colitis[14, 15, 18] without watery stools, relief occurred with elimination of allergenic foods. Blood in stools was absent in this series. In one child of 18 months, however, with diarrhea since birth, blood and mucus were constantly present. X-ray and proctoscopy ruled out ulcerative colitis and regional enteritis. With our minimal fruit-free elimination diet, the diarrhea, cramping, and blood and mucus gradually decreased over a period of four months, but it was necessary to continue the diet for eight more months until traces of blood and other symptoms disappeared. This case is not included in this series because pollen therapy and Piromen injections were given, although in our opinion the diet was entirely responsible for relief. In the last three years, symptoms have been perfectly controlled with the elimination of milk, wheat, chocolate, and fruits.

OTHER GASTROINTESTINAL SYMPTOMS

Diarrhea was the only evidence of gastrointestinal allergy in fourteen cases (Table II). In the sixteen others, one or more of the following symptoms occurred: The allergic epigastric syndrome,[22] evidenced by distention, burning, and pressure in the epigastrium and in some cases under the sternum or in the left chest, was present and relieved by the diet in six cases. Belching, sour stomach, nausea, and vomiting were present along with the allergic diarrhea. Canker sores,[15, 18] due nearly always to food allergy, in our opinion, were present in only one patient. All this emphasizes the presence of the shock tissues in the small bowel and especially in the large bowel in these cases.

TABLE II

SYMPTOMS	NUMBER OF CASES
Other Gastrointestinal Symptoms	
Allergic epigastric syndrome (pressure, distention, burning, etc.)	6
Nausea	6
Vomiting	2
Belching	6
Sour stomach	4
Canker sores	1
Additional Symptoms	
Fatigue	6
Body aching	4
Toxemia (allergic)	7 (2 severe)
Nervousness	7
Depression	5

TOXEMIA, FATIGUE, NERVOUSNESS, AND DEPRESSION

Fatigue, at times very severe, often with so-called toxemia, characterized by dopiness, confusion, and lack of concentration, occurred in seven patients. In several patients, especially in one child, weakness was very severe, associated with palpitation and even sweating. Relief of these symptoms with the elimination of allergenic foods illustrates the necessity of considering food allergy

as a possible cause of fatigue and toxemia,[20] which too often are ascribed to psychogenic causes. Nervousness, depression, and irritability in this group were controlled with the diet alone in about one-half of the cases. Sex hormones were given in the older women, when indicated.

OTHER MANIFESTATIONS OF ALLERGY

Their frequency[14, 15] in these cases of allergic diarrhea is shown in Table III. Their absence in fourteen cases illustrates the well-recognized fact that clinical allergy may be evident in only one shock organ or tissue, as the colon and/or small bowel. The family history for allergy and especially skin tests with foods may be negative also.

TABLE III. PERSONAL AND FAMILY HISTORIES OF ALLERGY

HISTORY	NUMBER OF CASES
Personal	
Bronchial	8
Nasal	7
Dermatitis	6
Hives	2
Headaches	6
(Negative in 10 cases)	
Family	
Gastrointestinal symptoms	3 (Duodenal ulcer in 1)
Diarrhea due to milk in mother, grandmother, and patient	1
Bronchial	9
Nasal	7
Cutaneous	6
(Negative in 11 cases)	

DIET HISTORY SUGGESTING FOOD ALLERGY

Milk was the food most frequently suspected as the cause of allergic diarrhea. It disagreed with or was disliked by eighteen of our patients. It was especially disliked by seven of the eighteen. It had always been vomited by two, and it was known to cause diarrhea in three. Egg disagreed with and was disliked by eight patients, being the sole cause of diarrhea in Case 2. Fruits, including tomatoes, seemed to cause diarrhea or gastrointestinal symptoms in fourteen; fish, in two; chocolate, in three; tomato, especially in one; wheat, in one; all cereals, in one; and soy, in one of the children. Cottonseed allergy receives discussion in Case 1. It must be recalled that such positive diet histories are not always indicative of specific allergy.

Drug allergy to barbiturates in two cases and to aspirin in one was evidenced.

POSITIVE SKIN TESTS

Although food allergy was the cause of the diarrhea in all these cases, scratch skin test reactions were negative in twenty-five cases, as is usual in chronic food allergy.[18] The reactions in four cases were slight. Large reactions

to foods were obtained in one child (Case 2). The few reactions to inhalants, moreover, were slight except for large reactions in three cases to pollens, which were responsible for seasonal hay fever and/or asthma.

	NUMBER OF CASES
Foods	4 (1– plus)—1 (3– to 8– plus)
Pollens	9 (3 gave large reactions)
Other inhalants	3 (1– plus)
House dust	4 (1– plus)
Fungi	1 (2– plus)

OTHER LABORATORY TESTS

Free hydrochloric acid was demonstrated in the stomach in sixteen cases. It was absent in two, although elimination diets controlled the diarrhea without the use of dilute hydrochloric acid. The test was not done in other patients because of the relatively rapid and excellent control of the diarrhea with the elimination diet. In eleven cases, the Diagnex test for hydrochloric acid was used, obviating intubation. Eosinophils, as reported by Nance,[11] were found in the stools of two children. Studies for them in stools of adults unfortunately were not done.

Stools were negative for parasites in twenty, and in ten cases stool analyses were omitted. *Amoebae histolytica* had been reported in two cases. Antiamebic therapy had failed to produce relief, and food allergy was the confirmed cause of the diarrhea.

Gastrointestinal roentgen-ray studies were negative in sixteen cases. A small-bowel study with a cold saline-barium mixture was negative in five cases. Colon roentgen-ray studies were negative in twenty-two cases, except for an ahaustric descending colon in one case and spastic colons in five cases. Such studies were omitted in the other cases because of obvious or early confirmed food allergy. Gall bladder roentgen-ray studies were negative in fifteen cases.

Proctoscopy was done in twenty patients. In five some erythema and edema were found and in one a few punctate probable ulcerations were seen. No blood or pus was present in these thirty cases.

Abdominal operations were remarkably infrequent. One hysterectomy for a fibroid had been done. Gall stones had been removed without relief of diarrhea and gastrointestinal symptoms in one patient; these symptoms were relieved, however, with the elimination diet. One patient had ten inches of the descending colon and upper sigmoid removed because of diverticula to relieve diarrhea and cramping for two previous years. Diarrhea continued, however, from the colostomy opening. Edema and erythema, but no ulcers or blood were present in the colon distal to the stoma. Colon roentgen-ray examination was negative. The diarrhea was entirely controlled with the elimination of all fruits, spices, and milk. The descending colon and the sigmoid have been rejoined and normal stools have continued for two years unless allergenic foods are eaten.

Psychogenic diarrhea had been suspected or diagnosed in twelve cases. In one case entirely controlled by the elimination of allergenic foods, hostility

to the patient's husband had been blamed! Thus, careful and adequate consideration of food allergy, in some cases pollen or other inhalant, or rarely drug allergy is important before diarrhea or other gastrointestinal symptoms are attributed to psychosomatic causes. In the other cases, either no cause had been found or previous study had not occurred. In four cases the allergenic foods had been self-determined.

DIAGNOSIS AND TREATMENT

Allergic diarrhea must be considered if parasites, infection, nutritional deficiencies, sprue, achylia, new growths, certain chronic diseases, and other recognized less common causes of diarrhea have been carefully excluded. Seasonal diarrhea, with or without other abdominal symptoms, due to pollen allergy[31] must also be remembered. When history, physical examination, laboratory and x-ray studies, and even empiric treatment apparently have ruled out all the above causes, psychogenic diarrhea too frequently is being blamed, as had occurred in twelve of our cases. This is not justified until adequate and experienced study of food allergy has been done.

Food allergy is probable if the diarrhea is nonseasonal. It is also suggested by dislikes for or symptoms from specific foods. The occurrence of other perennial manifestations of allergy or activation or occurrence of diarrhea or other possible allergic symptoms during the fall to late spring[16] favor food allergy. Colic and difficulties with feeding in childhood also suggest this cause. Skin reactions by the scratch or puncture methods are rarely positive to allergenic foods responsible for chronic allergic symptoms. Slight or even moderate skin reactions, especially by the intracutaneous method, frequently are nonspecific or do not reveal actual clinical food allergy. Thus, intracutaneous tests with food allergens are not routine in our work.

Diarrhea also occurs less frequently from pollen allergy.[31] Both food and pollen allergy, moreover, can concur.

When large skin reactions occur with the scratch or puncture method, total elimination of reacting foods may give complete relief. That all large positive reactions are not indicative of clinical food allergy is shown in Case 2. Thus, large as well as slight and negative reactions are fallible in the diagnosis of specific food allergy. In some patients, the elimination of foods that are disliked or avoided or which definitely disagree will relieve diarrhea and other allergic symptoms.

In most patients, however, scratch reactions are negative and dietary histories are of no help. In our thirty cases, the slight skin reactions to foods were of little or no help. In Case 2, only one of the several large reactions to foods indicated an allergenic food.

Thus, as in practically all patients with suspected food allergy, diet trial with our elimination diets[18, 29] is desirable, utilizing our standardized fruit- and cereal-free elimination diet. This eliminates practically all foods which we have found to be frequent causes of allergic diarrhea. This diet is also used to study possible food allergy in chronic ulcerative colitis,[19, 23] regional enteritis,[21] mucous colitis, the irritable or unstable colon, and other mani-

festations of gastrointestinal allergy. If some relief is not evident in ten to fourteen days, foods in the diet must be suspected. Then one of our minimal fruit-free elimination diets, such as rice, tapioca, white potato, lamb, chicken, soy, cottonseed oil, sugar, salt, and water, is justified.[22, 23] The inclusion of all or most of these foods in the three meals, with interval feedings of tapioca cooked with sugar and water and flavored with caramelized sugar or rice with plenty of sugar eaten on these foods and additional cube sugar eaten through the day, will furnish enough protein and calories to maintain weight. With synthetic vitamins and 2 to 3 grams of calcium carbonate daily, nutrition is maintained. Directions for the use of elimination diets, with required recipes for bakery products, emphasis on strict adherence to the diet, the time necessary for their use, addition of individual foods after relief is obtained, and other minimal elimination diets, will be found in our other publications.[15, 18]

All these patients have been carefully studied, of course, to rule out all possible diseases other than allergy.

FOODS CAUSING DIARRHEA

Milk allergy was most common, occurring in twenty-four cases. It was the sole cause in three patients. Milk and watermelon caused diarrhea in another patient. It is also so frequently the sole cause or an important cause of chronic ulcerative colitis[19, 23] due to food allergy that we have advised the total exclusion of milk for months and often for years in such patients. This frequency probably also occurs in regional enteritis,[21] in our opinion.

Fruits, including berries, melons, and tomatoes, were of next importance. After control of the diarrhea, ingestion of individual fruits has frequently shown allergy to all or individual fruits. Some patients tolerated some cooked but no fresh fruits.

Spices caused varying degrees of diarrhea, especially when allergy to fruits existed. Even minute amounts of these, as of any allergenic food, including inhalation thereof, may produce symptoms. Careful ingestion tests have indicated allergy to all vegetables in a few of our patients and to individual ones in others. Cooked and not raw vegetables at times were tolerated. Thus, peas, carrots, and string beans caused allergy in one case, and squash, celery, and artichokes caused allergy in another. White potato caused diarrhea in only two of these patients. Onions and, to a slight degree, garlic were the sole causes in one patient. They were incriminated with other foods in several other patients. Soybean intolerance occurred in one child. This intolerance prompted the senior writer, twenty years ago, to encourage the manufacture of strained liquid meats and to suggest the strained meat formula.[30] This formula is tolerated by practically all infants. Had many more infants been included in this series, other examples of soybean allergy or intolerance probably would have been encountered.

Allergy to egg is less common than to the above foods. It was the sole cause in Case 2; and, with milk and fruit allergy, it caused diarrhea in one

other case. Our experience also indicates that egg is a less common cause of manifestations in the gastrointestinal tract than in the respiratory or cutaneous tissues.

Wheat allergy was responsible, with other foods, in one patient and, with all other cereals and additional foods, in four other patients. Rice, corn, and oats were causative in a few cases.

Lamb was responsible, with other foods, in two patients. Pork, beef, and turkey were incriminated in a few patients. Gelatin was tolerated in fourteen patients in whose diets it was included.

Cottonseed oil caused diarrhea in one patient, corroborated by the resultant diarrhea when it was incorporated in bakery products and other foods without the patient's knowledge.

Peanuts and other nuts were suspected or not tolerated by several patients.

Foods eliminated in the following cases illustrate the similarities and variations in the final diets: *Case 1*—milk, egg, rye, corn, wheat, string beans, pit fruits; *Case 2*—milk, egg, fruits, spices, nuts, avocado; *Case 3*—milk, some fruits, spices; *Case 4*—milk, wheat, tomato, chocolate, coffee; *Case 5*—milk, fruits, rice, coffee, spices; *Case 6*—rice, corn, wheat, rye, potato, beef, lamb, pork, string beans, Lima beans; *Case 7*—milk, some fruits, spices; *Case 8*—milk, all vegetables, wheat, corn, pork, spices, soy; *Case 9*—egg, milk, wheat, chocolate, lettuce, and other leafy vegetables; *Case 10*—milk alone; *Case 11*—onion, garlic, coffee; *Case 12*—egg and probably chicken and peanuts.

TREATMENT AND CONTROL

The control of allergic diarrhea depends on the continued strict elimination of allergenic foods. Since canned milk and amino acids derived from casein have produced symptoms in many of our milk-sensitive patients, they have not been used in our diet trials.

As this diet is continued, tolerance for foods may increase in months or years. However, we have patients in whom milk, certain or all fruits, spices, and even vegetables and less frequently other determined allergenic foods have perforce been eliminated for years to prevent recurrence of diarrhea. In our practice, the disappearance of old and the appearance of new food allergies have occurred but this has not been the rule.

Desensitization by the oral method or with antigens containing allergenic foods has been disappointing.[15, 18] Reports of good results may have been in patients in whom the diagnosis of food allergy was made by positive skin reactions, especially by the intracutaneous method, without confirmation by the production of symptoms in the symptom-free patient. Thus, in Case 2 if desensitization had been done to beef, lamb, potato, and wheat, which our ingestion tests have proved were not responsible for the allergic diarrhea, success from such therapy might have been assumed. Desensitization to demonstrated allergenic foods, however, offers a continued future challenge which, because of the mass amounts, may never be possible.

Antihistamines have ameliorated gastrointestinal allergy in a few patients. Corticosteroids and corticotropin should benefit or control allergic diarrhea as

they often do in chronic ulcerative colitis, which is, in our opinion, an allergic disease. Relief of allergic diarrhea with these medicaments, however, would be unwise, as it is in chronic ulcerative colitis, unless adequate, persistent, and experienced antiallergic study and control are conducted, with the discontinuance of the sterocorticoids as rapidly as possible. The control of diarrhea in these thirty cases has resulted from the elimination of foods alone, without any antihistamines or corticosteroids, antispasmodics, antidiarrheals, or other drugs. In the initial stages of study, small doses of phenobarbital have been given briefly to a few patients. Absence of anemia necessitated no iron, B_{12}, or transfusions.

CASE REPORTS

CASE 1.—A woman of 56 years had had diarrhea for seven years, recurring for one to three days every ten to fourteen days, with two to five movements in each twenty-four hours. Much lower abdominal cramping, gas, and bloating, with at times embarrassing incontinence but no mucus or blood, had occurred. One normal daily movement was passed between attacks.

There was no history of previous gastrointestinal symptoms or possible clinical allergy, except for intermittent nasal blocking.

Diet history revealed suspicion of milk and its products, ginger, corn, nuts, pears, berries, and melons as activators of the diarrhea. The patient's drug and environmental histories suggested no allergy.

Family history showed eczema and hay fever in the son and hay fever and chronic gastrointestinal symptoms in the mother.

Physical examination, laboratory tests (including stool analysis for parasites), gastric analysis, and x-rays of the gastrointestinal tract (including the colon) and of the gall bladder had been done by two internists and also in a large diagnostic clinic, with negative results. Our diagnostic survey also was negative. The diarrhea had been attributed to "pressure of living" and emotional strain, due in part to a mother-in-law in the house.

Skin testing revealed slight or questionable reactions to wheat, egg, milk, tomato, and cocoa and a 2-plus reaction to mustard. She gave 2- and 3-plus reactions to grass pollens.

To study possible food allergy, our standardized fruit- and cereal-free elimination diet plus rice was ordered. In three weeks, no diarrhea had occurred. Then oats and cooked celery were added. Diarrhea remained absent. Her tongue no longer was coated, and she "felt better than in seven years." In the last year individual foods gradually have been added. The incriminated foods, with time of appearance of diarrhea, follow: milk, two to eight hours; onion, one-half hour; walnuts and almonds, one hour; cottonseed oil, two hours; coffee, one hour; bay leaf, three hours; mustard, one-half hour; Worcestershire sauce, one-half hour. Symptoms have lasted and decreased in two to twenty-four hours. Masked ingestion tests with milk and, because of the existing controversy, equivalent tests with cottonseed oil have confirmed them as causes of her diarrhea. Decision about other foods depended on two to several ingestions.

Comment.—This diarrhea, due especially to milk, had occurred intermittently for seven years, even though milk and its products had been ingested in only moderate amounts. Attacks developed suddenly, with constant fear of possible incontinence. Diet and family histories were negative for allergy. Slight reactions to foods did not correlate with the finally determined allergenic foods. Positive reactions to pollens were not indicative of clinical allergy.

There was much frustration because of lack of relief and the fact that there was no explanation except psychosomatic causes after surveys by excellent internists. This illustrates the too frequent ignoring of food allergy in differential diagnosis and the value of our fruit- and cereal-free elimination diet[18] in the study and control of food allergy.

CASE 2.—A 1-year-old child was seen two and one-half years ago because of loose, odorous stools which had begun when the patient was 4 months old; there had been a moderate fever for one day. The diarrhea had persisted for five to eight days every ten to twenty days for eight months, occurring daily for the last two and one-half months. Paratyphoid bacilli had been cultured from a commercial dried egg yolk fed to the child and also from one stool specimen, but the diarrhea continued in spite of drug therapy. Fever had never recurred. Weight gain, nutrition, and health (except for the diarrhea) were normal. Additional studies, including hemograms, cultures of the urine and the stools, and stool analyses for parasites, were made with negative results in a teaching hospital and at a large Midwestern clinic.

Since food allergy had not been studied and since the family history revealed hives in the mother, death of an uncle from asthma in childhood, eczema in the father, and hay fever in a grandmother, the senior writer studied such possible allergy. Puncture tests revealed the following positive reactions when first seen. One year after rapid initial and continued relief from the elimination diet, they were repeated.

May 29, 1953		*March 15, 1954*	
Egg	8-plus	Egg	8-plus
Beef	2-plus	Beef	2-plus
Codfish	2-plus	Lamb	4-plus
Potato	2-plus	Potato	3-plus
Peanut	2-plus	Chicken	4-plus
Chicken	3-plus	Wheat	2-plus
		Peanut	6-plus

Physical examination was negative. Hemogram was normal except for 87 per cent lymphocytes in 1953, with a reduction to 73 per cent in 1954.

In the initial study of possible food allergy, a minimal fruit-free elimination diet was ordered, containing our strained beef formula (Gerber's),[30] rice, oats, strained lamb, puréed carrots, peas, string beans, white and sweet potato, sugar, salt, synthetic multiple vitamins, and water. Diarrhea disappeared in two days, recurring with fewer stools in twelve days. Thereafter, one daily formed stool was passed for four months in spite of the addition of wheat, bacon, beef, squash, beets, practically all cooked fruits, raw banana, and finally milk. Then ½ teaspoonful of egg produced diarrhea in one-half hour, reaffirmed on two other occasions in the next four months. During the last two years no diarrhea has occurred except when a baby sitter gave the patient cookies containing egg.

Comment.—It is probable that the diarrhea which occurred when the patient was 4 months old was due to allergy to the egg protein first given in the canned yolk. Paratyphoid infection seems unlikely because the slight fever on the first day did not recur and because of the absence of malaise or any symptoms except diarrhea thereafter. Food allergy has caused foul stools in other patients in our series and in those recorded in the literature. Egg had been given as such or in cooking for the eight months before we saw this patient.

Skin testing by the puncture method gave the recorded skin reactions. Because of the very large skin reaction to egg, it was, of course, eliminated from the diet and also eliminated from the home. The mother was advised to guard the child against the smell of egg in other homes and eating places. Potato and beef were included in the initial diet in spite of the 2-plus reactions. Tolerance to them and also to lamb and wheat, which gave additional reactions at the end of one year, has been amply confirmed. Because of the frequency of clinical allergy to peanuts, to which a large skin reaction was obtained, and because of the demonstrated allergy to egg, peanuts and chicken have not been included in the diet to date. Thus, our long emphasis on the fallibility of the skin test,[14, 15, 18] even when large reactions are obtained, is illustrated. The necessity of diet or ingestion trial to prove clinical allergy to foods giving both negative and positive reactions is demonstrated.

In our experience, clinical allergy to egg giving large reactions may disappear along with the skin reaction in four to seven years. Too often clinical allergy continues much

longer. Desensitization by ingestion, as already discussed, usually fails and may produce severe and even shock reactions.

This case illustrates the all-too-common failure to remember the many manifestations of food allergy and to study it with the recognized fallibility of the skin test in mind. Of interest is the incrimination of egg instead of milk, the latter being the most common food to cause allergic diarrhea. Even though the family history and the skin reactions had not indicated allergy, the study of food allergy would have been necessary.

CASE 3.—A woman of 53 years had passed six to ten watery stools for two to seven days with varying intervening constipation every ten to twenty days for eight years. In addition, burning, distention, and pressure in the epigastrium, with pressure under the sternum and moderate belching and occasional nausea, had occurred. She had been fatigued all her life. For several years, aching in the extremities and moderate depression had been present.

Diet history revealed increased diarrhea from milk and fruits, neither of which, however, had been entirely eliminated.

Lifelong recurrent headaches associated with nausea and at times with vomiting had occurred. Family history showed no predisposition to allergy except to eczema.

Blood count, urinalysis, stool examinations for parasites, and x-ray examinations of the gastrointestinal tract, including the colon, had been negative on three different occasions. Achylia had been found, but hydrochloric acid was ineffectual.

Much medical therapy had failed, and psychoneurosis had been blamed by three physicians. Our duplication of the laboratory and x-ray studies revealed similar findings.

Skin testing gave 1-plus reactions to several pollens, other inhalants, and dust.

To study food allergy, our minimal fruit-free elimination diet was given. In two weeks the diarrhea, epigastric distress, and fatigue were less, and in four weeks they were absent. During the next four months all foods were gradually added, and only milk, all fruits, all condiments, and coffee reproduced the diarrhea. During the last two years the diarrhea, constipation, headaches, fatigue, and depression have been controlled except with increasingly rare breaks in the diet. She has resumed work as a practical nurse and is "enjoying life again."

Comment.—Milk, fruits, and spices were responsible for the diarrhea and other invaliding symptoms, thus disproving the former diagnosis of psychoneurosis. Dilute hydrochloric acid was not given.

CASE 4.—A man of 25 years suddenly developed assumed intestinal flu in March, 1950. Eight to ten daily watery movements, with much cramping and no blood or mucus, continued until we saw him in September. Physical examination and laboratory studies, including stomach analysis and examination of the stools for parasites, were negative in two hospitals. Stools occurred three to four times in the morning and two to three times in the evening; none occurred at night. Fatigue and weakness had occurred almost daily. Empiric antiamebic therapy had been ineffectual.

There was no history of personal or family allergy or chronic disease.

Diet history revealed a lifelong dislike for milk. Various foods, such as lettuce, spinach, chard, and corn, appeared undigested at times in the stools.

Skin testing with all important inhalants and foods gave negative results. Hemogram was normal except for 16,000 leukocytes, which fell to 9,300 in three weeks after the diarrhea had ceased with the elimination diet.

To study possible food allergy, we ordered our fruit- and cereal-free elimination diet plus rice. In three days diarrhea decreased, and in five days there was one formed stool daily. Cereals, fish, fruits, other vegetables, egg, milk, tea, and coffee were gradually added in the next two and one-half months. Milk especially and more than one cup of coffee daily reproduced diarrhea. After five years, these still have to be eliminated.

Comment.—Milk, which had been distasteful for years, was the major cause of this diarrhea. Empiric antiamebic therapy had been given, as is the case in many of these

so-called idiopathic diarrheas. The personal and family histories were negative for allergy. No one of the seven physicians he had consulted previously had suggested allergy as a cause.

SUMMARY

1. Diarrhea from food allergy in twenty-six adults and four infants and children is reported. Diarrhea and other gastrointestinal symptoms due to pollen allergy and diarrhea resulting from chronic ulcerative colitis and regional enteritis due to allergy are not included.

2. The literature containing many reports of colic and diarrhea due to food allergy in infants and children and in relatively few adults is reviewed.

3. Because of the usual negative laboratory tests, including stool analyses for parasites and x-ray studies of the stomach, small intestine, and colon, and the failure of various drugs and diets, functional diarrhea due to psychoneurosis is a common and unfortunate diagnosis in cases due to food allergy.

4. A personal or family history of clinical allergy may be absent. The gastrointestinal tract, especially the colon, in these patients may be the sole shock organ of allergy.

5. Although many patients give a diet history indicating dislikes and definite or suspected disagreements and resultant symptoms from specific foods, such foods often are not responsible for the diarrhea or other associated symptoms due to allergy.

6. Skin testing by the scratch or puncture method infrequently reveals positive reactions to any or all causative allergenic foods. Large reactions need careful consideration. The ingestion tests on the symptom-free patient may reveal allergy to none or to one or more reacting foods, as illustrated in Case 2.

7. When a diet excluding foods causing large skin reactions or foods suspected through diet history fails to relieve the diarrhea, then our standardized fruit-free elimination diet or our minimal fruit-free elimination diet is advised.

8. Milk, fruits, and spices have been most frequently responsible for allergic diarrhea in our patients. Allergy to many other foods, as determined by individual ingestion tests in the symptom-free patient, also occurs, as discussed in this article.

9. This allergic diarrhea, including tenesmus and even incontinence, may be so persistent and chronic and at times associated with other symptoms of gastrointestinal allergy, headaches, allergic fatigue, and toxemia, that semi- and even complete invalidism may result for months or even years.

REFERENCES

1. Andresen, A. F. R.: Gastro-Intestinal Manifestations of Food Allergy, J. M. Soc. New Jersey **31**: 402, 1934.
2. Browning, W. H.: Allergic Diarrheas, Tri-State M. J. **7**: 1426, 1935.
3. Clein, N. W.: Cow's Milk Allergy in Infants, Ann. Allergy **9**: 195, 1951.
4. Collins-Williams, C.: Acute Allergic Reactions to Cow's Milk, Ann. Allergy **13**: 415, 1955.
5. Dees, Suran: Practical Aspects of Allergy, J. Pediat. **37**: 695, 1950.
6. Friedenwald, J., and Morrison, S.: Food Allergy in Its Relation to Gastro-Intestinal Disorders, Am. J. Digest. Dis. & Nutrition **1**: 100, 1934.

7. Greer, D.: The Treatment of Food Allergy in Young Infants, Texas State J. Med. **29**: 370, 1933.
8. Hansel, F.: Clinical Allergy, Philadelphia, 1953, W. B. Saunders Company.
9. Kerley, C. S.: Allergic Manifestations to Cow's Milk, New York State J. Med. **36**: 1320, 1936.
10. Laroche, G., Richet, Fils C., and Saint-Girons, F.: Alimentary Anaphylaxis, Translated by Rowe, Berkeley, 1930, University California Press; French edition, Paris, 1919.
11. Nance, F. D.: Stool Eosinophilia in Gastro-Intestinal Allergy in Infancy, J. Pediat. **33**: 313, 1948.
12. Piness, G., and Miller, H.: Food Factor in Allergy, Colorado Med. **30**: 405, 1933.
13. Ratner, B.: Treatment of Milk Allergy and Its Basic Principles, J. A. M. A. **105**: 934, 1935.
14. Rowe, Albert H.: Food Allergy, Philadelphia, 1931, Lea & Febiger.
15. Rowe, Albert H.: Clinical Allergy, Philadelphia, 1937, Lea & Febiger.
16. Rowe, Albert H.: Seasonal and Geographic Influences on Food Allergy, J. ALLERGY **13**: 55-60, 1941.
17. Rowe, Albert H.: Clinical Allergy in the Nervous System, J. Nerv. & Ment. Dis. **99**: 834, 1944.
18. Rowe, Albert H.: Elimination Diets and the Patients' Allergies, ed. 2, Philadelphia, 1944, Lea & Febiger.
19. Rowe, Albert H.: Chronic Ulcerative Colitis—An Allergic Disease, Ann. Allergy **7**: 727-751, 819, 1949.
20. Rowe, Albert H.: Allergic Toxemia and Fatigue, Ann. Allergy **8**: 72-79, 84, 1950.
21. Rowe, Albert H., Rowe, Albert, Jr., and Uyeyama, K.: Regional Enteritis—Its Allergic Aspects, Gastroenterology **23**: 554-571, 1953.
22. Rowe, Albert H., Rowe, Albert, Jr., and Uyeyama, K.: Allergic Epigastric Syndrome, J. ALLERGY **25**: 464-471, 1954.
23. Rowe, Albert H., Rowe, Albert, Jr., and Uyeyama, K.: Chronic Ulcerative Colitis and Regional Enteritis—Their Allergic Aspects, Ann. Allergy **12**: 387-402, 1954.
24. Rowe, Albert H., Rowe. Albert, Jr., and Uyeyama, K.: Chronic Ulcerative Colitis Due to Pollen Allergy With Six Case Reports, Acta med. scandinav. **152**: 139, 1955.
25. Rubin, M. I.: Allergic Intestinal Bleeding in the New-Born, Am. J. M. Sc. **200**: 385, 1940.
26. Schloss, O. M.: Allergy in Infants and Children, Am. J. Dis. Child. **19**: 433, 1920.
27. Shannon, Ray: Anaphylaxis to Food Proteins in Breast-Fed Infants, Minnesota Med. **5**: 137, 1922.
28. Talbot, F. B.: Role of Food Idiosyncrasies in Practice, New York J. Med. **17**: 419, 1917.
29. Vaughan, W., and Black, H.: Clinical Allergy, Philadelphia, 1954, W. B. Saunders Company.
30. Rowe, Albert, Jr., and Rowe, Albert H.: Strained Meat Formulas in Allergic Diseases of Infants and Children, California Med. **81**: 279, 1954.
31. Rowe, Albert H., Rowe, Albert, Jr., and Young, E. James: Gastro-Intestinal Symptoms Due to Pollen Allergy, Ann. Allergy (to be published).

ASTHMA AND RHINITIS FROM INSECT ALLERGENS

I. Clinical Importance

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ALLERGY to insects has been known for a long time. Anaphylactic death from a bee sting was reported at least as early as 200 years ago,[1] and probably as early as 2641 B.C., when, according to hieroglyphics found at his tomb, King Menes of Egypt was stung to death by a wasp or hornet. A number of such cases of anaphylactic shock or death have been described since. Severe reactions to the bites or stings of other insects have also been noted. Isolated instances of asthma or rhinitis from insects as inhalant allergens have been observed. These insects include the May fly,[2, 2a] caddis fly,[3] mushroom fly,[4] aphid,[5] bedbug,[6] locust,[7] bee,[8] house fly,[9] moth,[10, 10a] daphnia,[11] Mexican bean weevil,[12] beetles,[13] sewage filter flies,[14] and mites.[15] Many of these cases have been occupational, as in laboratory workers, beekeepers, and mushroom growers. Some insects, such as the caddis and May flies, have been demonstrated as important causes of respiratory allergy for a few days during the summer in special areas. However, the concept that insects† and other forms of small animal life may be a major cause of respiratory allergy has not been seriously considered.

Several factors have combined to arouse our interest in this subject. We, as well as others, have encountered a number of patients whose symptoms are only partly or not at all explained by current ideas of the etiology of respiratory allergy. Some of these patients present seasonal exacerbations but fail to react to pollen or molds, while the seasonal patterns of others cannot be explained solely on their pollen and mold allergy. Some of the patients with symptoms of unexplained etiology react to silk and/or May fly. Previously we had not considered the May fly reactions clinically significant if the symptoms did not coincide with the short May fly season. Positive skin tests to silk,‡ observed quite commonly for several decades, have never been satisfactorily explained on the basis of exposure to silk fabrics. It was also noted that a patient who reacted to one of the insects often reacted to others. It be-

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†In this article we shall use the term "insect" loosely, as certain of the arthropods mentioned are not true insects according to classification.

‡Extracts of silk pupa gave stronger reactions than those of the cocoon.

came apparent that the silk reactions in most cases were related to insect sensitivity rather than sensitivity to silk textiles. During the last several years we employed desensitizing injections of May fly or silk extract in a small number of seasonal patients whose respiratory allergy could not be explained by other causes. The results were gratifying. This led us to the next step.

Authoritative sources indicate the presence of hundreds of millions of arthropods per acre of surface soil.[16] It was thought possible that soil dust or dust from other organic matter might contain substances of insect origin. We embarked, therefore, on a more serious program of clinical and experimental observations on insect allergy. Our first problem was to obtain insects in sufficiently large quantities to represent as many different groups as possible. Thus far, we have been only partly successful in this respect. We were able to obtain about twenty different varieties from various sources, but with many of the materials the quantity was inadequate for experimental work or desensitization or even for diagnostic tests in a large series of patients.

The insects were extracted in the usual manner and patients were tested routinely by scratch test. Patients were tested with those antigens available at the time, so that not every patient was tested with every insect. Results of testing, the symptoms, reactions to noninsect antigens, the antigens used in treatment, and the results of treatment were recorded on punch cards and tabulated.

RESULTS OF CLINICAL STUDIES

Our clinical observations disclosed several points of interest. Many of our patients, especially some of those whose symptoms were not entirely explainable on any other etiological basis, reacted on scratch test to insect antigens. Those who gave positive skin tests to one insect usually reacted to a number of insects, although to some more often than to others.

TABLE I. MANIFESTATIONS IN 130 PATIENTS WITH POSITIVE SKIN TESTS TO INSECT ANTIGENS

SYMPTOM	NO. OF PATIENTS	PER CENT
Asthma	54	41
Hay fever or perennial rhinitis	110	85
Atopic dermatitis	11	8
Conjunctivitis	4	3

Table I shows a listing of the symptoms in a series of 130 patients who gave positive skin tests to insect allergens. The high incidence of nasal symptoms is evident. The vast majority had either rhinitis or asthma, or both. It should be added that twenty-two of these 130 patients were children under the age of 12 years.

The histories of these 130 patients were analyzed for their seasonal trends and for evidence of the clinical significance of the skin reactions to insect antigens. Table II presents a summary of the major findings. Twenty-five had perennial symptoms without obvious seasonal variation. Forty-four had

seasonal symptoms only, the "season" varying in different individuals but being frequently as early as April and as late as November. In twenty-six of these the types of pollen and/or mold reactions could explain the seasonal pattern without necessarily attaching any clinical significance to the positive skin tests with the insect antigens. In eighteen out of these forty-four, however, the mold and pollen reactions could not explain the particular season of the individual's symptoms. For example, patient J. B. had no reactions to any antigens other than insects, her symptoms occurring from April to August, inclusive. Patient I. C. had symptoms in July, August, and September, while the only positive skin test other than that to insects was obtained with house dust. Patient E. reacted to ragweed pollen and insects but the season of June to September obviously could not be explained by ragweed alone. Patient H. reacted to ragweed and grass pollen in addition to insects, but the seasonal aggravation occurred from April to September, inclusive.

TABLE II. INADEQUACY OF POLLEN AND MOLD REACTIONS AS SOLE EXPLANATION OF SEASONAL TRENDS (ANALYSIS OF 130 PATIENTS REACTING BY SCRATCH TEST WITH INSECT ANTIGENS)

Perennial symptoms only		25
Seasonal symptoms only		44
Seasonal pattern compatible with their pollen and mold reactions	26	
Seasonal pattern not explainable solely on pollen and mold reactivity	18	
Perennial symptoms plus seasonal aggravation		61
Seasonal pattern compatible with their pollen and mold allergy	34	
Seasonal pattern not explainable solely on pollen and mold sensitivity	27	
Total number of patients whose seasonal pattern or seasonal aggravation is not explainable solely on their pollen and mold allergy		45

There were sixty-one patients who had perennial symptoms with the addition of unquestioned seasonal aggravation. In thirty-four of these the seasonal phases were compatible with their pollen and/or mold allergy. In twenty-seven, however, it was clear that pollen and mold allergy alone could not explain the particular individual's seasonal part of the clinical picture. For example, Mrs. K. had perennial rhinitis and asthma, worse from May to October, and the only skin reactions were to house dust and insects. F. M. reacted to dust, ragweed, and insects, and the symptoms were increased from June to September, inclusive.

Table II shows that, of the 130 patients reacting with insect allergy, the seasonal pattern with seasonal symptoms or with perennial symptoms aggravated during the summer months cannot be explained solely by pollen and mold allergy in 45. It is in these cases, particularly, where the presumptive evidence of clinical allergy to insects is strongest.

An analysis of the skin reactions, other than those to insect antigens, in the group of 130 patients who gave positive skin tests to insect antigens is shown in Table III. The highest percentage of reactions (69 per cent) was to

house dust (Endo's). Ragweed pollen and molds were also frequent reactors. Only nine patients of this group reacted solely to insects. Four patients reacted to shrimp. Two of these were tested with daphnia (water flea), a crustacean, and both gave positive tests.

TABLE III. POSITIVE SKIN TESTS (OTHER THAN TO INSECTS) IN 130 PATIENTS GIVING SKIN REACTIONS TO INSECTS

ALLERGENS	NO. OF PATIENTS	PER CENT
House dust (Endo)	90	69
Molds	72	55
Ragweed	83	64
Grass	41	32
Tree	9	7
Epidermals	50	38
Foods	19	15

Table IV shows the results of skin tests in this group with different insect antigens. Only those positive by scratch tests were included. The size of the reactions was similar to that in pollen cases, giving what are commonly designated as 2+ or 3+ reactions. As mentioned previously, not all patients were tested with each antigen because of the changing availability of our materials as the observations progressed. A number of other insects were tested but are not included in the table, since the number was too small for

TABLE IV. PERCENTAGE OF REACTIONS WITH VARIOUS INSECT ANTIGENS IN 130 PATIENTS GIVING POSITIVE REACTIONS TO INSECT ANTIGENS ON SCRATCH TEST

INSECT	NO. REACTING/NO. TESTED	PER CENT
May fly	88/127	69
Silk pupa	90/118	76
Silk cocoon	64/114	56
Silk pupa, cocoon or both	104/125	83
Silk pupa, cocoon or May fly	125/130	96
Grasshopper	20/80	25
Ant eggs	51/79	65
House fly	24/49	49
Mosquito (*Aedes aegypti*)	12/35	34
Honey bee	18/46	39
Daphnia (water flea)*	39/80	49
Mediterranean fruit fly	16/27	59
Melon fly	13/28	46

*Contaminated with insects, type undetermined.

evaluation purposes. Included in this group are caddis fly, aphid, codling moth, oriental fruit flies, oriental rat flea, mushroom fly, and cockroach. Reaction to these insects generally followed the same pattern as to those listed in the table. Every serum thus far obtained from a patient giving good scratch tests to insect antigens gave a good reaction on passive transfer.

Skin tests made with acetone-precipitated fractions of three or four samples of soil gave negative tests in several insect-sensitive patients.

The results of desensitization with insect antigens are shown in Table V. The earlier cases were treated with either May fly or silk antigens; the more

TABLE V. RESULTS IN 26 PATIENTS RECEIVING DESENSITIZATION THERAPY WITH INSECT ANTIGENS

RESULT	NO. OF PATIENTS
Poor	7
Moderate	6
Good	13

recent cases have been given a mixture of several antigens. We have the impression that the results are encouraging. A still larger group of patients have not yet been observed or treated long enough to enable us to appraise results. In still other instances, the concomitant treatment with other antigens makes the interpretation difficult.

CASE REPORTS

The following brief case reports illustrate some of the features associated with insect allergy.

CASE 1.—I. C., a 63-year-old physician from Indiana, consulted us on Oct. 9, 1953, because of allergic rhinitis of three years' duration and asthma of one year's duration, beginning in July and ending in September. Increased numbers of eosinophils were found in his blood and sputum. Skin tests failed to show positive reactions to pollens or molds, but were positive to May fly, silk, and house dust. Desensitization treatment with May fly resulted in early improvement, and the following season he was practically symptom free. In July, 1955, his symptoms returned in part. The addition of silk and house dust extracts to the treatment resulted in improvement again.

CASE 2.—T. A., a 46-year-old woman seen by us on March 27, 1950, had a history of many years of itching, inflammation and discharge from the eyes, and some nasal stuffiness. The symptoms were perennial, but worse from May to October. This was aggravated after automobile trips or when visiting her farm on week ends. Skin tests showed a good reaction to silk but to no other antigens. At that time we made the following note on her record: "If no response to symptomatic treatment, to consider desensitization with silk antigen." The patient did not return until March 28, 1955, five years later. Her complaints were identical except that they had become more troublesome. With a fuller realization of the significance of the silk reaction, we retested her with a number of insect antigens. Positive reactions were obtained with silk, May fly, ant eggs, and daphnia. Treatment with extract of silk pupa and May fly resulted in rapid and marked alleviation of symptoms.

CASE 3.—E. H., a 31-year-old man from Alabama, consulted us on June 24, 1947, with a history of hay fever for ten years from June to September. Although skin tests made previously had been negative, he had been treated with pollen and mold extracts without relief. Our tests showed strong reactions by scratch test to silk, May fly, and house dust, and moderate reactions to intracutaneous tests with corn and wheat smut, trichophyton, and yeast. Treatment with extracts of silk, house dust, and smut gave excellent results the following season.

IMMUNOLOGIC OBSERVATIONS

Since there exist tens of thousands of insect species, the diagnostic and therapeutic problem becomes complicated unless we can determine to what extent the antigen of one species may represent others. Our first step, therefore, was to begin a study of the relationship of antigens in several insects with

which we had done clinical work. In choosing the insects, we had to be guided in large part by availability of material. The procedures planned were as follows: precipitin and cross precipitin tests; precipitin absorption tests; gel diffusion analysis (Oudin tubes[17] and Jennings' triangular plates[18]); cross reaction by anaphylactic shock, Schultz-Dale technique and asthma from aerosolized antigen in passively and actively sensitized guinea pigs; skin tests in rabbits with the aid of trypan blue; and neutralization studies of reagins in human subjects. In these studies the following antigens were used: May fly, pupa of silk moth, ant eggs, daphnia, and house dust.

Since most of these studies are not completed at this time, we only indicate the trends and some of the difficulties encountered and will report our findings more fully later. Precipitin and gel diffusion tests showed some cross precipitation between May fly and silk and, to some extent, ant eggs. None of the insect antisera reacted to Endo's house dust. In anaphylaxis, difficulties have been encountered in that the control nonsensitized animals gave anaphylactic-like reactions on injections of May fly or silk antigen. Whether this is a true, naturally acquired sensitivity or an anaphylactoid reaction to the specific insect or to a microorganism common to the insect and guinea pig remains to be determined. It apparently is not due to a histamine-like substance in the antigen solution, since the removal of diffusible substances by dialysis has not removed this anaphylactic-like property.

COMMENT

Although we believe that insects are a major cause of respiratory allergy, the difficulties of demonstrating this are several. The air cannot be analyzed by the usual methods for amorphous insect dust as it can be examined for pollens and molds. The majority of patients reacting to insects also react to other allergens, thus presenting obstacles to absolute proof of the role of the insect reactions. However, where seasonal symptoms are involved, in a significant percentage (43 per cent) the reactions to insect antigens appear to furnish the missing link to complete the seasonal etiology. The fact that conclusive evidence for clinical significance of the skin tests to insects cannot be obtained in the remainder should not be disturbing, since a similar difficulty arises in substantiating other seasonal allergy, such as grass or ragweed pollen reactions in the presence of mold allergy. Thus far, we have failed to obtain conclusive skin tests with soil dust in insect-sensitive patients; it is possible that our method is at fault. Nevertheless, reactions to inhalant allergens in general have a high index of reliability in designating a state of clinical allergy. We would infer that this also applies to insect allergens. In the light of our observations, there is justification to the suggestion made a number of years ago[19] that in the South many of the cases of seasonal respiratory allergy not reacting to pollen or molds may be due to insect allergy.

The relationship of antigens of various insects has not yet been ascertained. It is possible that the tendency for the insect-sensitive patient to react to a large variety of insects may constitute evidence of ability to become sensitized to a variety of inhalants of the same general type rather than to a single common antigen. Cross reactivity must be a factor also, since most of patients have not had the opportunity to become exposed to such insects as the yellow fever mosquito, Mediterranean fruit fly, and others. The possibility must also be considered that the cross reactivity may represent a common contaminant, such as the microbial content of the gastrointestinal tract of the insects.

This is only a preliminary report. There is much to be done in this field. Immunologic studies will require long and extensive work. Studies of the chemical nature of the antigens are necessary. The origin of the material to which the patient becomes exposed is still not definitely settled. Other forms of small animal life, such as other arthropods, nematodes, and other denizens of the soil, must be considered.

SUMMARY

Insects and arthropods probably constitute a major cause of respiratory allergy. This is supported by the frequent reactions to insects on scratch tests, the inability to find other etiological factors to explain completely the symptoms in many of these patients, the probable prevalence of insect substances in the air, and the encouraging results obtained by desensitization. Preliminary findings on immunologic aspects are noted, but extensive work is needed to determine the antigenic relationship and chemical characteristics of the antigens.

REFERENCES

1. Desbret: Observations sur les Maladies epidemiques qui regnerent a Cusset et dans ses environs, sur la fin de l'annee 1762, pendant le courant de 1763 et dans le commencement de 1764, J. Medecine, Chirurgie, Pharmacie, etc. **23:** 141-216, 1765.
2. Wilson, H.: Preliminary Report of a Case of Sensitization to the May-Fly (Ephemera), J. A. M. A. **61:** 1648, 1913.
2a. Figley, K. D.: Asthma Due to the Mayfly, Am. J. M. Sc. **178:** 338, 1929.
3. Parlato, S. J.: The Sand Fly (Caddis Fly) as an Exciting Cause of Allergic Coryza and Asthma. II. Its Relative Frequency, J. ALLERGY **1:** 307, 1930.
4. Kern, R. A.: Asthma Due to Sensitization to a Mushroom Fly (*Aphiochaeta agarici*), J. ALLERGY **9:** 604, 1938.
5. Gaillard, G.: The Aphid—An Insect Allergen, J. ALLERGY **21:** 386, 1950.
6. Sternberg, L.: A Case of Asthma Caused by the Cimex Lectularius, M. J. & Rec. **129:** 622, 1929.
7. Frankland, A. W.: Locust Sensitivity, Ann. Allergy **11:** 445, 1953.
8. Ellis, R. V., and Ahrens, H. G.: Hypersensitiveness to Air-Borne Bee Allergen, J. ALLERGY **3:** 247, 1932.
9. Jamieson, H. C.: The House Fly as a Cause of Nasal Allergy, J. ALLERGY **9:** 274, 1938.
10. Randolph, H.: Allergic Response to Dust of Insect Origin, J. A. M. A. **103:** 560, 1934.
10a. Urbach, E., and Gottlieb, P. M.: Asthma From Insect Emanations; Report of a Case Due to Moths, J. ALLERGY **12:** 485, 1941.
11. Way, K. D.: Water Flea Sensitivity; Case Report, J. ALLERGY **12:** 495, 1940.
12. Wittich, F. W.: Allergic Rhinitis and Asthma Due to Sensitization to the Mexican Bean Weevil (*Zabrotes subfasciatus*, Boh.), J. ALLERGY **12:** 42, 1940.
13. Sheldon, J. M., and Johnson, J. H.: Allergy to Beetles (*Coleoptera*), J. ALLERGY **12:** 493, 1940-41.
14. Ordman, D.: Sewage Filter Flies (Psychoda) as a Cause of Bronchial Asthma, South African M. J. **20:** 32, 1946.

15. Ancona, G.: Asma Epidemico da "Pediculoides ventricosus," Policlinico (sez. med.) **30**: 45, 1923.
16. United States Department of Agriculture: Insects, in the Yearbook of Agriculture, Washington, D. C., 1952, U. S. Government Printing Office.
17. Oudin, J.: Methods in Medical Research, Chicago, 1952, The Yearbook Publishers, Inc., vol. 5.
18. Jennings, R. K.: Diffusion-Precipitin Studies of the Complexity of Antigen Mixtures; II. The Number of Zones Formed by One Antigen, J. Bact. **67**: 565, 1954.
19. Weil, C. K.: Summer Hay Fever of Unknown Origin in the Southeast, J. ALLERGY **11**: 361, 1939-40.

ANAPHYLACTIC SHOCK IN THE MOUSE VACCINATED WITH HEMOPHILUS PERTUSSIS

IV. Studies on the Adrenal Gland

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PREVIOUS reports[1, 2] have described a technique whereby anaphylactic shock can be elicited regularly in both the white mouse and the rat, animals which usually are difficult to sensitize. A high per cent mortality is consistently attained on challenging animals which previously have received a vaccine of *Hemophilus pertussis* Phase I organisms together with a sensitizing antigen. At the present time the mechanism of this enhancement of sensitization is not understood. It does not appear that the mechanism can be entirely accounted for by the "schlepper" effect of the cells.[3] In addition, the speculation[4] that *H. pertussis,* by its inherent toxicity, injures the adrenal gland and in effect produces an adrenalectomized, and hence a highly sensitive, animal does not seem warranted.[5] The present report, concerning itself with endocrine and histopathologic studies of adrenals of mice sensitized thereby, attempts to establish the role of this gland in the pertussis-vaccinated animal.

PROCEDURES

Effect of Adrenalectomy on Sensitization.—Adrenalectomized female white mice of the Swiss-Webster strain were maintained throughout the course of the experiment on a 1 per cent salt solution and received, in addition, a daily subcutaneous injection of 0.1 ml. of aqueous adrenal cortical extract (ACE).* These mice were divided subsequently into two groups, with Group 1 receiving 1 mg. of crystalline egg albumin intraperitoneally and Group 2 receiving 1 mg. egg albumin as a mixture with either 8×10^8 *H. pertussis* Phase I organisms or 1 ml. of a saline extract of the cells. It has been shown previously[3] that the saline extract of *H. pertussis* is as effective as the intact organisms in enhancing sensitization. A third group, acting as an additional control and consisting of adrenalectomized animals injected with 1 mg. egg albumin only, did not receive the daily maintenance dose of ACE. On the tenth day subsequent to the immunization, all the animals of the three groups were challenged with an intravenous injection of 1 mg. egg albumin given in 0.1 ml. of solution.

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*The biologic activity of the ACE used in this study was equivalent to approximately 0.2 mg. compound F per milliliter.

Results: The mortality results due to the anaphylactic shock can be seen in Table I. They indicate that *H. pertussis* is capable of enhancing the production of sensitivity over and above that obtained by the antigen alone in adrenalectomized mice. A 96 per cent mortality was observed for that group of animals receiving the egg albumin and *H. pertussis,* as compared to a 25 per cent mortality for the group sensitized with egg albumin only. The mortality of 41 per cent observed for that group of animals not receiving the daily injection of ACE indicates that ACE is a somewhat effective replacement therapy, as noted by the partial suppression of sensitization of the adrenalectomized mice.

TABLE I. SENSITIVITY OF ADRENALECTOMIZED MICE

	INTRAPERITONEAL SENSITIZATION		
	ACE		NO ACE
INTRAVENOUS CHALLENGE	EGG ALBUMIN ONLY	EGG ALBUMIN AND H. PERTUSSIS	EGG ALBUMIN ONLY
Mortality	25/98 (25%)	97/101 (96%)	12/29 (41%)

The above adrenalectomized mice were maintained on 1 per cent sodium chloride and 0.1 ml. adrenal cortical extract (ACE) daily. Sensitization was accomplished with 1 mg. egg albumin intraperitoneally and challenge with 1 mg. egg albumin intravenously after ten days.

Effect of H. pertussis on 17-Ketosteroid Excretion.—Four groups, each consisting of two young female white rats, weighing 175 to 200 grams, were arranged in metabolism cages. The total urine excreted over a seventy-two hour period was collected from each group and the 17-ketosteroids were determined and recorded as the average total milligrams excreted per twenty-four hours.* Two such seventy-two hour control pre-sensitization periods determined the base line of milligram of steroid excreted. Two groups of rats were then injected intraperitoneally with 1 ml. of a 1:10 dilution of horse serum and two groups received a suspension of 5×10^{10} *H. pertussis* organisms in the same volume of antigen. During the subsequent fifteen days, urine from each group was collected over three seventy-two hour periods and the average total milligram of 17-ketosteroid excreted per twenty-four hours was calculated. On the fifteenth day, all eight rats were challenged by the intravenous injection of 1 ml. of a 1:10 dilution of horse serum.

TABLE II. AVERAGE TOTAL MILLIGRAM STEROIDS EXCRETED PER TWENTY-FOUR HOURS FOR EACH THREE-DAY PERIOD

GROUP	PREINOCULATION		POSTINOCULATION		
		Inoculated With Horse Serum			
I	0.12	0.06	0.20	0.12	0.13
II	0.10	0.07	0.09	0.08	0.14
		Inoculated With Horse Serum and H. Pertussis			
III	0.09	0.13	0.16	0.11	0.18
IV	0.19	0.11	0.15	0.16	0.19

Each group consists of two rats, each weighing 175 to 200 grams.

*We are indebted to the Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts, for the steroid analyses.

Results: None of the four animals sensitized by horse serum only died of anaphylactic shock, but all four rats that received *H. pertussis* in addition succumbed. This indicated that sensitization had, indeed, been effected. Table II indicates that no significant difference was noted between the sensitized and nonsensitized groups of animals with respect to the average total milligram of 17-ketosteroids excreted per twenty-four hours.

Histopathologic Studies of Adrenals of Sensitized Mice.—Three groups of mice were studied in this series. The mice of Group 1 were injected with 1 ml. egg albumin intraperitoneally, those of Group 2 received 10^{10} *H. pertussis* Phase I organisms only, whereas those of Group 3 were inoculated with a mixture. Two animals of each group were sacrificed on the second, fourth, seventh, tenth, fifteenth, twenty-first, and twenty-fifth days, respectively, following the inoculation. The adrenal glands were removed, fixed in Zenker's solution, sectioned, and stained. Individual sections were stained with either phloxine-methylene blue or methyl green-pyronine. Careful microscopic examination of the sections failed to reveal any essential differences between the adrenal glands of the three groups. Each showed normal medulla and cortex, with the latter presenting the usual three zones. The cells of each layer appeared normal and were comparable with respect to size, shape, and staining reactions.

DISCUSSION

It has been observed that either adrenalectomy[6] or vaccination with *H. pertussis*[7] will increase the susceptibility of mice to histamine. It has been reported also that anaphylactic sensitivity is enhanced under similar circumstances.[1, 8] The apparent parallelism makes it tempting to suggest[4] that the action of the toxic vaccine on the adrenals results in the enhancement of sensitivity to histamine and of antigenic sensitization. Recent studies by Gauthier, Loew, and Jenkins[9] support the concept that enhancement to histamine is through some mechanism other than impairment of adrenal function. The results described in this report seem to indicate that dysfunction of the gland does not play a significant role in anaphylactic sensitization either.

An essential difference in the experimental procedure should be pointed out, which may account for the difference in the results of this report and that of Dougherty[8] relative to the increase of anaphylactic sensitivity following adrenalectomy. In the latter studies, adrenalectomy was carried out *after* immunization and following an incubation period; this usually occurred just prior to anaphylactic challenge. In the present study, the mice were adrenalectomized *prior* to sensitization. Under these latter conditions, a mortality of 41 per cent was obtained by anaphylactic challenge for a group of mice inoculated with egg albumin only, while that group similarly sensitized but maintained on ACE gave a mortality of 25 per cent. ACE has the capability of acting as a replacement therapy to some degree for, although these mortality values are admittedly greater than that obtained for the intact mouse inoculated with egg albumin only (5 per cent), sensitization was somewhat suppressed by ACE in the adrenalectomized group (25 per cent versus 41 per cent mortality).

Moreover, the 96 per cent mortality, by comparison, obtained with the group of ACE-maintained, adrenalectomized mice receiving a mixture of antigen with *H. pertussis,* becomes significant and seems to be related directly to the injection of the organisms. The intact animal sensitized in similar fashion exhibits a 74 per cent mortality.[3] This effect of *H. pertussis* is striking, even though the mortality values observed for the experimental groups of adrenalectomized animals are greater than that for groups of intact animals. Regeneration of adrenal rests, adventitious glands, or compound F effect need not be considered as pertinent, for these factors would rather tend to make the differences more striking by repressing even more the mortality of the control groups.

The level of urinary 17-ketosteroid excretion indicates that no significant alteration attended either inoculation of the rats with horse serum or sensitization with a mixture of the antigen and *H. pertussis.* Although these observations can be interpreted as indicating that there has been little, if any, interference with the "normal" secretory function of the adrenals and hence little serious impairment of its metabolism, nevertheless, additional tests of adrenal function would be required for supporting evidence. Little is actually known concerning the amount of toxic injury required and it may be presumed by implication that damage severe enough to alter sensitization so markedly would be reflected by an alteration in steroid excretion. Previously surgical ablation of the adrenals was required to cause such a high mortality in so drastic a measure of sensitivity as anaphylactic death in the mouse. The failure to observe any changes in cellular structure or configuration of the adrenal glands following *H. pertussis* inoculation seems to be indicative that toxic changes have not taken place at the microscopic level, at least.

The mechanism by which *H. pertussis* enhances anaphylactic sensitivity still requires further investigation. The mitigation apparently is not by a direct effect on the adrenal gland, although cortisone (in relatively large amounts) has been observed to prevent fatal anaphylactic shock in the pertussis-vaccinated[2] as well as intact[10] mouse. One needs consider other levels of *H. pertussis* function.

SUMMARY

1. *Hemophilus pertussis* organisms have the ability of enhancing sensitization in the adrenalectomized mouse maintained on adrenal cortical extract.

2. The mechanism by which sensitization is enhanced does not seem to be a result of the direct toxic effect of the organisms on the adrenal gland.

3. The amount of 17-ketosteroids excreted in the urine is not altered by inoculating the animal with *H. pertussis.*

4. Histopathologic studies fail to reveal any changes in the cellular structure of the adrenal gland following inoculation.

REFERENCES

1. Malkiel, S., and Hargis, B. J.: Anaphylactic Shock in the Pertussis Vaccinated Mouse, Proc. Soc. Exper. Biol. & Med. **80**: 122, 1952.

2. Malkiel, S., and Hargis, B. J.: Anaphylactic Shock in the Pertussis-Vaccinated Mouse, J. ALLERGY **23:** 352, 1952.
3. Malkiel, S., and Hargis, B. J.: Anaphylactic Shock in the Mouse Vaccinated With *Hemophilus Pertussis.* III. Antigens, Antibody and Passive Transfer Studies, J. Immunol. **71:** 311, 1953.
4. Kind, L. S.: The Altered Reactivity of Mice After Immunization With *Hemophilus pertussis* Vaccine, J. Immunol. **70:** 411, 1953.
5. Malkiel, S.: Active Anaphylaxis in the Pertussis Inoculated White Mouse, Proc. VIth Internat. Cong. Microbiol. **2:** 265, 1953.
6. Weiser, R. S., Golub, O. J., and Hamre, D. M.: Studies on Anaphylaxis in the Mouse, J. Infect. Dis. **68:** 97, 1941.
7. Parfentjev, I. A., and Goodline, M. A.: Histamine Shock in Mice Sensitized With Hemophilus pertussis Vaccine, J. Pharmacol. & Exper. Therap. **92:** 411, 1948.
8. Dougherty, T. F.: The Protective Role of Adrenal Cortical Secretion in the Hypersensitive State, in Moe, G. K.: Pituitary Adrenal Function, Washington, D. C., 1950, American Association for the Advancement of Science, p. 79.
9. Gauthier, G. F., Loew, E. R., and Jenkins, H. J.: Histamine Sensitivity of Adrenalectomized and Pertussis-Treated Mice, Proc. Soc. Exper. Biol. & Med. **90:** 726, 1955.
10. Nelson, C. T., Fox, C. L., Jr., and Freeman, E. B.: Inhibitory Effect of Cortisone on Anaphylaxis in the Mouse, Proc. Soc. Exper. Biol. & Med. **75:** 181, 1950.

THE ROLE OF C-REACTIVE PROTEIN IN ALLERGIC INFLAMMATION

Relationship Between the Acute Phase Response and the Antibody Titer

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THERE is ample evidence, from animal experiments and from immunization studies in human beings, that wide differences in antibody production occur among subjects receiving identical dosages of a given antigen. It has been demonstrated that a large proportion of patients with proved uncomplicated streptococcal infection fail to develop antistreptolysin O (ASO) antibodies.[1, 2] Similarly, although the attack rate for rheumatic fever has been demonstrated to be related to the magnitude of the antibody response to beta hemolytic streptococcal infection,[1] more than 20 per cent of the patients with acute rheumatic fever fail to produce, early in the course of the disease, definite elevation in antibodies to the extracellular antigens of group A streptococci.[3] These observations suggest the hypothesis that a relationship may exist between the "acute phase response" to the antigenic contact and the subsequent antibody production. This hypothesis finds support in the experimental observations of Wood[4] that the production of antibodies in the rabbit is closely related to the amount of C-reactive protein (C-RP) appearing in the blood in response to the injection of antigen. In fact, C-reactive protein, an abnormal protein which forms a precipitate with the nontype-specific pneumonococcal C polysaccharide and migrates by electrophoresis with the beta globulins, has been shown to be a very sensitive indicator of the "acute phase serum."[5, 6]

The present work was undertaken to study the relationships existing between the early appearance of C-RP in the "acute phase serum" of patients whose throat culture showed the presence of group A (Lancefield) streptococci and the subsequent immune response and to analyze and discuss the significance of the immune response to streptococcal infection and of C-RP values during the clinical course of the rheumatic fever.

MATERIALS AND METHODS

Routine throat cultures and serial determinations of the serum titer of streptococcal antibodies were performed at regular intervals in 103 patients

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at Mount Sinai Hospital and LaRabida Sanitarium. Beta hemolytic streptococci were isolated by direct inoculation of 5 per cent sheep blood agar. All strains of beta hemolytic streptococci were grouped and typed by standard methods.[6] Determinations of the serum titer of antistreptolysin O were made by the Rantz and Randall modifications[7] of the original method of Todd.[8] Antistreptokinase (ASK) determinations were made by the quantitative method of Christensen.[9] Erythrocyte sedimentation rates were measured by the method of Wintrobe, with corrections for variations of the hematocrit according to standard tables. Tests for the C-reactive protein were performed routinely by the capillary method as described by Goldin and Kaplan.[10] For the quantitative determination of the serum content in C-RP, we used a gel diffusion method described previously by us.[11] Antibody determinations were made on sera which had been stored at –20° C. The sera were obtained by serial bleedings done at weekly intervals. In order to minimize variations due to technical errors, stored samples of serum were thawed and the titers of antibody in the specimen were determined simultaneously on the same day.

The patients included in this study were grouped as follows:

1. Patients who developed tonsillar or pharyngeal exudates and who were found to have ten or more colonies of type 14, group A (Lancefield) streptococci on throat culture. Of this group, patients were excluded who gave a past history of rheumatic fever and presented signs of rheumatic heart disease or showed evidences of suppurative complication during their illness. All the patients with tonsillar or pharyngeal exudates were treated with antibiotics until complete disappearance of typable group A streptococci from throat cultures. Forty-three patients received daily injections of 300,000 units of procaine penicillin for a period ranging from seven to twelve days; fourteen patients received 600,000 units of procaine penicillin in oil with 2 per cent aluminum monostearate every other day for four to five doses.

2. Patients admitted to the Mount Sinai Hospital and LaRabida Sanitarium in the acute stage of rheumatic fever. All the patients included in this group met the criteria of Jones[12] for the diagnosis of rheumatic fever. From our survey, we purposely omitted the patients with "chorea" or with "erythema marginatum" as isolated manifestations of the rheumatic process.[13, 14] The treatment of these patients did not follow a definite regimen. Seventeen patients received hormone therapy. Eight young patients (6, 16, 26, 27, 28, 30, 38, and 41) within the first week of rheumatic carditis were treated with cortisone by mouth in daily doses of 300 mg. for four to six weeks. After this period, the drug was administered in doses of 12 mg. daily for varying periods of time. Four patients (31, 32, 42, and 43) were treated with prednisone in daily doses of 30 mg., maintained for five days. The doses were then gradually reduced over an additional period of thirty days. The other five patients received varying doses

of corticotropin, corticotropin followed by cortisone, or cortisone alone. The maximum daily dose of corticotropin was 60 mg. maintained for four days, and of cortisone, 200 mg. maintained for four days. The doses were then gradually decreased over a period of twenty-seven to forty days. Twenty-nine rheumatic patients without evidence of carditis were treated with salicylate. The dosage schedule was satisfactorily constant: 0.10 Gm. per kilogram of body weight daily for three days, then 0.08 Gm. per kilogram daily for seven days, and finally 0.05 Gm. per kilogram for three weeks. After this, salicylate was reduced to 1 Gm. daily for additional six weeks. The patients were observed until most evidences of the disease had subsided and through a convalescent period of several months thereafter.

RESULTS

Antibody Titer Following Acute Streptococcal Pharyngitis.—Fifty-seven patients with acute exudative pharyngitis, whose throat culture developed ten or more colonies of group A beta hemolytic streptococci, were studied. Our survey was limited to the type 14 that was found to be the most common occurring in group A streptococcal infections. Furthermore, the heterogeneity of the infecting streptococcal strain may affect both the incidence and the degree of antibody response. Seventeen patients were between the ages of 5 and 10 years, twenty-four were between 10 and 20, and sixteen were over 20 years old. The serum samples for the determinations of C-RP and antibody titer during the acute phase response were obtained within four days of the onset of the clinical manifestations. C-RP was found present in varying

TABLE I. CORRELATIONS BETWEEN C-REACTIVE PROTEIN RESPONSE AND ANTIBODY TITER FOLLOWING INFECTION WITH GROUP A BETA HEMOLYTIC STREPTOCOCCI, TYPE 14

NO. OF PATIENTS WITH GROUP A TYPE 14 STREPTOCOCCUS INFECTION	C-RP PRESENT IN SERUM DURING ACUTE PHASE RESPONSE (MG./C.C.)	ANTIBODY TITER (UNITS/C.C.)					
		ONSET OF ACUTE PHARYNGITIS		AFTER 4 WEEKS		AVERAGE RISE	
		ASO	ASK	ASO	ASK	ASO	ASK
5	Below 0.003	112	270	138	256	26	–
8	0.003 to 0.030	175	320	288	583	113	263
7	0.030 to 0.070	122	412	295	730	173	318
22	0.070 to 0.100	227	301	487	792	260	391
15	over 0.100	165	380	417	720	252	340
57		180	336	387	668	208	347

amounts in fifty-two out of fifty-seven patients. The five patients with negative C-RP were children less than 12 years old. Antibiotic therapy was instituted as soon as the bacteriologic diagnosis was established. Complete disappearance of the group A streptococci from the throat cultures was obtained within one week in fifty-five patients. Two patients still harbored the infecting type of streptococcus three weeks after the onset of the acute pharyngitis. As is apparent in Table I, in the patients with negative C-RP in the acute phase serum the ASO and ASK titers did not increase in the four weeks following the acute streptococcal pharyngitis. The patients who de-

veloped C-RP in response to the group A streptococcal pharyngitis were the ones who developed high antibody titers. The average increases of ASO and ASK titers determined four weeks after the acute pharyngitis were, respectively, 208 and 347 units per cubic centimeter. Furthermore, a roughly quantitative relationship was observed between the intensity of the "acute phase response," as evidenced by the presence in the serum of increasing amounts of C-RP, and the subsequent rise of antibody titers (Fig. 1).

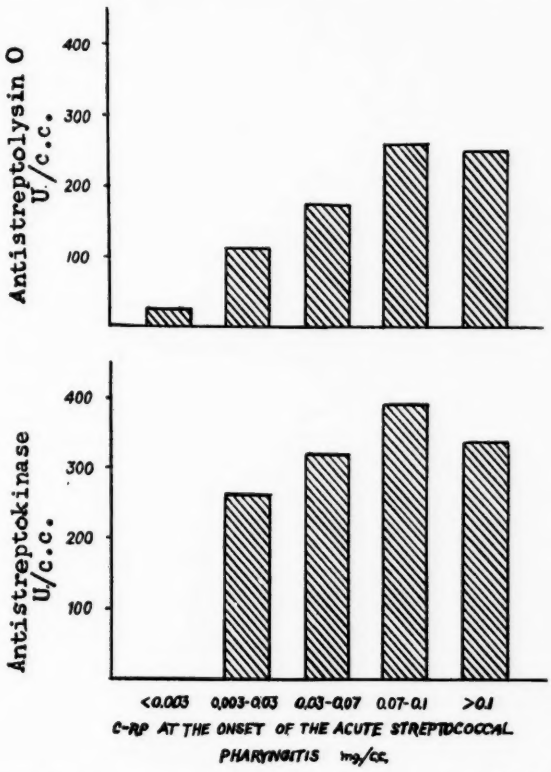

Fig. 1.—Average rise of antibody titers in fifty-seven patients within four weeks of the onset of acute streptococcus pharyngitis, in relation to the values of C-RP present in the "acute phase serum."

Correlation Between C-Reactive Protein and Antistreptolysin O and Antistreptokinase Titers in Acute Rheumatic Fever.—The values of C-RP and the ASO and ASK titers were determined in forty-six patients with clinical evidences of acute rheumatic fever according to the criteria of Jones. C-RP was found present in varying amounts in the serum of all forty-six patients during the acute rheumatic attack. It still remained positive in decreasing amounts in thirty-two patients after one week, in sixteen patients after three weeks, and in eight patients after five weeks from the onset of the acute rheumatic fever, being a reliable indicator of the rheumatic activity (Table II). C-RP was found present again for a few days in eight out of forty-six patients as a "rebound" phenomenon when the therapy was interrupted. The ASO and

TABLE II. ANTISTREPTOLYSIN O AND ANTISTREPTOKINASE TITERS, C-REACTIVE PRO-

PATIENT	1 TO 3 WEEKS BEFORE ACUTE RHEUMATIC FEVER				ONSET OF ACUTE RHEUMATIC FEVER				1			
	ASO	ASK	THROAT CULTURES	C-RP*	ASO	ASK	THROAT CULTURES	C-RP	ASO	ASK	THROAT CULTURES	C-RP
1. M. K.					500	640		+	500	1,280		+
2. M. M.					833	1,280	Neg.	+++	833	640	Neg.	+
3. G. T.					333	320	A-1	++	500	320	Neg.	+
4. P. D.					333	160	Neg.	++	333	80		Neg.
5. K. A.					333	320	Neg.	++	333	320		Neg.
6. G. G.					625	640	Neg.	+++	625	160		Neg.
7. V. M.					333	320		++++	500	640		++
8. J. S.	333	160	Neg.	Neg.	100	40	A-5	+++		160		
9. B. E.					500	640	Neg.	+	333	640		+
10. T. T.					250	160	Neg.	+	250	320		+
11. D. N.	333				333	640	A-18	++++	500	1,280	A-18	++
12. D. L.					500	1,280	Neg.	++	625	1,280		++
13. L. V.					333	320	Neg.	++	250	160		++
14. R. L.†	500	320	Neg.	Neg.	333	640	Neg.	+++	625	320		Neg.
15. G. L.†					166	80	A-14	++++	333	160	A-14	+
16. B. B.					250	160	Neg.	++	250	320		Neg.
17. B. Z.					333	320	Neg.	+++	333	640	A-14	++
18. J. C.	333	1,280	Neg.	Neg.	500	640	Neg.	+	500	640		+
19. K. Z.					625	640	Neg.	++	500	640		+
20. W. W.†	250	640	A-5	Neg.	333	320	Neg.	+++	250	320	Neg.	Neg.
21. L. W.	625	640	Neg.	Neg.	333	320	Neg.	+++	250	320	Neg.	+++
22. E. L.					625	640	Neg.	+	625	640	Neg.	+
23. G. M.	333	640		Neg.	333	320	Neg.	+++	250	320	Neg.	+
24. A. L.	250	320	A-14	Neg.	250	160	A-12	++++	500	160	Neg.	Neg.
25. L. C.†	333	80	Neg.	Neg.	125	80	A-14	++++	500	40	Neg.	+
26. L. C.	333	320		Neg.	333	320	Neg.	+	250	160		Neg.
27. L. K.					833	1,280	Neg.	+++	625	640	Neg.	+
28. A. K.†	500			Neg.	500	640	Neg.	+++	500	640	Neg.	+
29. L. F.	500	640		Neg.	333		A-18	+++	500	160	Neg.	++
30. W. E.	333	320	Neg.	Neg.	166	80	Neg.	+++	333	160	Neg.	+
31. J. C.	500	320	Neg.	Neg.	333	320	Neg.	++++	500	640	Neg.	Neg.
32. R. L.					333	640	A-19	+++	500	640	Neg.	+
33. L. V.					125	80	A-14	++++	333	320		+
34. M. K.	500	640	Neg.	Neg.	333	320	Neg.	+++	333	640		+
35. G. H.					250	160	Neg.	++	250	160		++
36. M. W.					333	320	Neg.	+	250	320		+
37. W. Z.					833	1,280	Neg.	+	833			Neg.
38. S. W.					250	160	A-19	++++	500	640	A-19	+
39. R. J.					125	80	Neg.	++++	333	160		++
40. J. K.					100	160	Neg.	++	250	320		Neg.
41. M. K.					125	80	Neg.	+++	333	160		+
42. C. P.					250	320	Neg.	++	333	320		++
43. J. A.					166	160	A-19	++++	333	320	Neg.	Neg.
44. A. C.					250	160	Neg.	++	250	320	Neg.	Neg.
45. A. F.					333	320	A-14	+	500	640	Neg.	+
46. H. L.					333	320	Neg.	+	500	320		Neg.

*C-RP. + = 0.003 to 0.030 (mg./ml.). +++ = 0.070 to 0.100 (mg./ml.)
++ = 0.030 to 0.070 (mg./ml.). ++++ = over 0.100.
†Recurrent rheumatic carditis with congestive heart failure.
ASO = Antistreptolysin O (units/c.c.).
ASK = Antistreptokinase titers (units/c.c.).

ASK titers showed large individual differences. However, as is evident in Table II, the courses of the ASO and ASK titers were similar during the rheumatic disease. The average titers of forty-six patients at the onset of the rheu-

TEIN, AND THROAT CULTURES IN FORTY-SIX PATIENTS WITH ACUTE RHEUMATIC FEVER

WEEKS FOLLOWING ONSET OF ACUTE RHEUMATIC FEVER												
3				5				10				
ASO	ASK	THROAT CULTURES	C-RP	ASO	ASK	THROAT CULTURES	C-RP	ASO	ASK	THROAT CULTURES	C-RP	TREATMENT BESIDES ANTIBIOTICS
500	1,280		Neg.	625	1,280		Neg.	333	640		Neg.	ASA
833	640		Neg.	833	1,280	Neg.	Neg.	500	1,280		Neg.	ASA
500	320	Neg.	+	833	320	Neg.	Neg.	500	320		Neg.	ASA
333	80	Neg.	+	500	80		Neg.	333	40	Neg.	Neg.	ASA
500	320		Neg.	500	160		Neg.	250	160			ASA
1,250	1,280		+	833	640		Neg.	833	320		Neg.	Steroid
620	1,280	Neg.	+	625	1,280	Neg.	+	650	1,280		Neg.	Steroid
625			Neg.	500			Neg.	125			Neg.	ASA
625	640		Neg.	625	640		Neg.	250	640		Neg.	ASA
333	640		+									ASA
625	1,280	Neg.	++	500	640	Neg.	++	250	640	Neg.		ASA
625	1,280	Neg.	+	625	1,280		Neg.	500	1,280		Neg.	ASA
500	320		Neg.	625	320		Neg.	500	160			ASA
833	640	Neg.	+	500	640		Neg.	250	160			ASA
500	320	Neg.	Neg.					500	160	Neg.	Neg.	ASA
333	1,280	Neg.	Neg.					333	640			Steroid
125	640	A-14	Neg.	333	320		+	250	320		Neg.	Steroid
833	640		Neg.	833	640		Neg.	625	640		Neg.	ASA
	1,280			500	1,280		Neg.	500	1,280		Neg.	Steroid
				500	640		Neg.	333	640		Neg.	Steroid
250	640		+++	500	640	Neg.	++	333	640		Neg.	ASA
625	640		Neg.	625	640		Neg.	333	320		Neg.	ASA
333	320		Neg.	500	160		Neg.	333	160		Neg.	ASA
625	320		Neg.	625	320	Neg.	+	500	160		Neg.	ASA
833	160	Neg.	Neg.	500	160	A-14	+	625	80	Neg.	Neg.	ASA
333	160		Neg.	333	320		Neg.	125	320		Neg.	Steroid
833	1,280	Neg.	Neg.	625	640		Neg.	500	640		Neg.	Steroid
500	640		+	500			Neg.	125	320			Steroid
500	160	A-18	+					250	80		Neg.	Steroid
333	320		Neg.	333	160		Neg.	250	320		Neg.	Steroid
500	640		Neg.	333	640		Neg.	500	640		Neg.	Steroid
500	640		Neg.		320			333	160		Neg.	Steroid
625	640		Neg.	625	1,280		Neg.	500	1,280		Neg.	ASA
500	320		Neg.	625	320		Neg.	500	160		Neg.	ASA
333	160		Neg.	333	160		Neg.					ASA
333	640		Neg.	333	1,280		Neg.	250	1,280		Neg.	ASA
1,250	1,280		Neg.	625	1,280		Neg.	500	640		Neg.	ASA
625	640	Neg.	Neg.	500	640		Neg.	333	320			Steroid
500	320		Neg.	500	320		Neg.	500	320		Neg.	ASA
500	640		+	250	640		Neg.	250	640		Neg.	ASA
333	160		+	333	160		Neg.	333	80		Neg.	Steroid
333	320		++	250	320		+	250	320		Neg.	Steroid
333	640		Neg.	250	640		+	250	640		Neg.	Steroid
333	160		Neg.	250	80		Neg.	250	80		Neg.	ASA
625	320		Neg.	500	160		Neg.	250	160		Neg.	ASA
500	640		Neg.	333	640		Neg.	125	320		Neg.	ASA

matic attack were, respectively, 354 and 411 units per cubic centimeter. Three weeks following the onset of the rheumatic attack, the average values were 536 ASO units per cubic centimeter and 535 ASK units per cubic centimeter. Five weeks following the acute attack, the values were 556 ASO units per cubic centimeter and 506 ASK units per cubic centimeter. Within ten weeks of the rheumatic attack, the ASO and ASK titers were, respectively, 352 and

435 units per cubic centimeter (Table III). As is indicated in Fig. 2, in nine patients with C-RP values ranging from 3 to 30 mcg. per cubic centimeter during the acute phase, the average ASO titer was 412 units per cubic centimeter with a subsequent rise at five weeks' interval of 55 units. In the same patients the acute ASK titer was 488 units per cubic centimeter with a subsequent rise of 54 units per cubic centimeter. On the other hand, in ten patients with C-RP values over 100 mcg. per cubic centimeter, the average ASO and ASK titers at the time of the acute phase were 225 units per cubic centimeter and 372 units per cubic centimeter, with a subsequent rise at five weeks' interval of 407 and 236 units per cubic centimeter.

TABLE III. CORRELATIONS BETWEEN C-RP RESPONSE AND ANTIBODY TITER IN FORTY-SIX PATIENTS WITH ACUTE RHEUMATIC FEVER

NO. OF PATIENTS	C-RP VALUES AT ONSET OF ACUTE RHEUMATIC ATTACK (MG./C.C.)	ANTIBODY TITER (UNITS/C.C.)							
		AT ONSET OF ACUTE RHEUMATIC ATTACK		AFTER 3 WEEKS		AFTER 5 WEEKS		AFTER 10 WEEKS	
		ASO	ASK	ASO	ASK	ASO	ASK	ASO	ASK
1	Below 0.003	833	–	1,250	–	500	–	625	–
9	0.003 to 0.030	412	488	523	587	467	542	308	440
11	0.030 to 0.070	323	400	429	489	466	454	366	413
15	0.070 to 0.100	394	413	549	536	553	494	389	376
10	Over 0.100	225	372	579	608	632	608	420	552
46		354	411	536	535	556	506	352	435

In fourteen patients we were able to obtain the ASO and ASK titers in a period of one to three weeks before the recurrence of a rheumatic attack. The average ASO values for these fourteen patients were, respectively, 402 units per cubic centimeter and 456 units per cubic centimeter before the rheumatic attack, 313 units per cubic centimeter and 331 units per cubic centimeter at the onset of the acute attack, and 516 units per cubic centimeter and 508 units per cubic centimeter five weeks after the acute attack. The lowest average antibody values were obtained at the onset of the acute rheumatic attack, concomitant with the highest values of C-RP (0.082 mg. per milliliter). The subsequent rise of ASO and ASK titers were parallel to the decrease of C-RP content in the serum (Fig. 3). Of fifty-four patients with acute rheumatic fever, twenty-nine were treated with acetylsalicylic acid and seventeen with steroids (cortisone, prednisone, ACTH) for varying periods of time. For the patients treated with acetylsalicylic acid, the average ASO and ASK titers at the onset of acute rheumatic fever, respectively, were 343 units and 422 units per cubic centimeter, with a subsequent average rise of 211 and 378 units per cubic centimeter at the determinations performed after five weeks. For the patients treated with steroids, the acute average ASO titer was 416 units per cubic centimeter, with a subsequent rise of 64 units per cubic centimeter after five weeks. For the same patients, the average acute ASK titer was 411 units per cubic centimeter with a subsequent rise of 98 units per cubic centimeter after five weeks. Nine of these fifty-four patients showed the presence of typable group A streptococci in the throat culture made at the onset of an acute rheumatic fever episode (Table III). In patient B. Z. (No. 17),

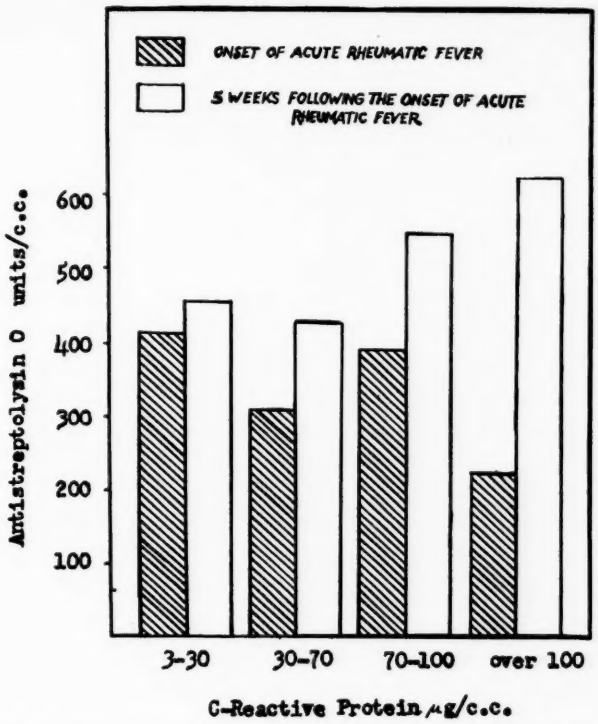

Fig. 2.—Course of antistreptolysin O titer in relation to the values of C-RP present in the serum at the onset of acute rheumatic fever.

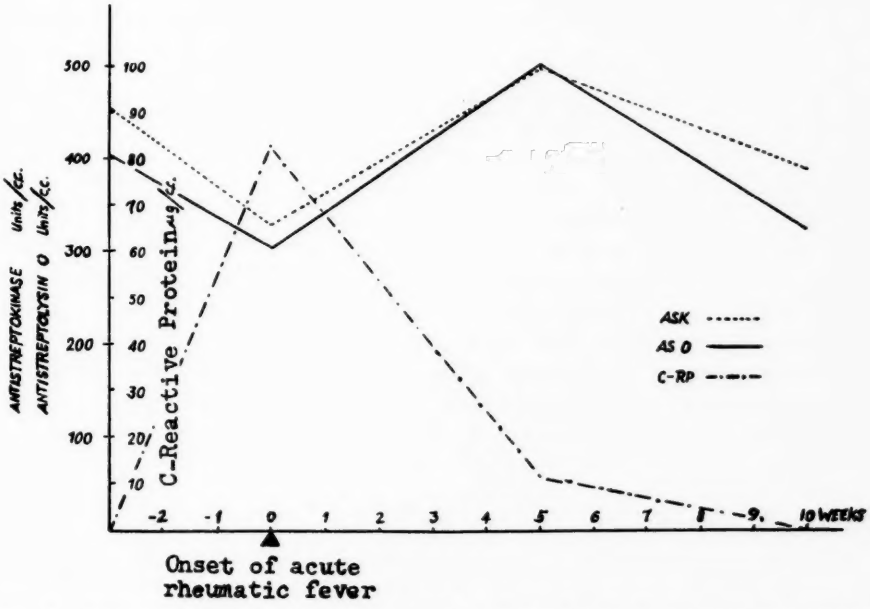

Fig. 3.—Course of ASO and ASK titers and of C-RP values in fourteen patients with recurrent acute rheumatic fever.

group A streptococci type 14 were detected in the throat culture performed one week after the onset of acute rheumatic fever, and remained present during the following three weeks. In patient L. C. (No. 25), group A streptococci, type 14, were present in the throat culture performed on the first day of the acute rheumatic fever attack. Subsequent throat cultures, obtained at weekly intervals, were negative. Group A streptococci of the same type 14 were again present in a throat culture performed five weeks after the onset of the acute episode.

DISCUSSION

The results of our study clearly indicate that a consistent positive relationship exists between the early production of C-RP at the time of the contact of the antigen with the host and the subsequent production of a high titer of antibody. Only the patients who showed an early response to the streptococcal infection by the production of the abnormal C-RP later developed significant levels of ASO and ASK antibodies. Furthermore, a roughly quantitative correlation seems apparent between the amounts of C-RP appearing in the serum in response to the streptococcal infection and the subsequent rise in antibody titer. No rises of ASO or ASK titers were evident at the follow-up examinations in five young patients, who did not produce detectable amounts of C-RP during the phases of streptococcal pharyngitis. On the other hand, average increases of 257 ASO units per cubic centimeter and 372 ASK units per cubic centimeter were observed in thirty-seven patients who produced more than 0.070 mg. per cubic centimeter of C-RP in the acute phase response to the streptococcal infection. Obviously, the properties of the streptococcal strain involved may affect both the percentage of patients showing an antibody response and the degree of antibody response. Evidences have been presented[13] showing that there exists a relationship between the capacity of a strain to elaborate streptokinase and the production of antistreptokinase by the patients infected with it. For these reasons, our survey was limited to the patients whose throat culture indicated the presence of group A beta hemolytic streptococci, type 14. The study performed in forty-six patients with acute rheumatic fever indicate that C-RP is always present in varying amounts in the acute phase of the rheumatic fever, being a reliable indicator of inflammatory activity. Furthermore, our survey adds additional evidences to support the contention that immunologic evidence of antecedent streptococcal infection may be found in every new attack of rheumatic fever. The highest antibody titers are approached within three weeks of the onset of acute rheumatic fever attack if proper therapy maintains the patient free from streptococcal infections. As is apparent in Table III and in the series of fourteen patients represented in Fig. 3, a marked decrease in ASO and ASK titers is observed concomitant to the presence of C-RP in the serum. Furthermore, a roughly quantitative relationship is apparent between the amount of C-RP appearing in the serum during the acute phase and the subsequent increase of antibody titer.

The importance of C-RP in antibody production has been repeatedly suggested. The experiments performed in rabbits by Wood[14] demonstrated that substances like adjuvants which induce a C-RP response are able to enhance

the production of antibody to antigen introduced at a separate site. Also, the degree of the inflammatory reaction has been considered the factor influencing the production of antibody.[15] However, it has been suggested that the changes which occur in antibody response with advancing age are, in reality, a function of repeated experiences with the organism. Furthermore, the studies of Catanzaro and associates[16] indicated that a continued antigenic stimulation is necessary for the antibody response to group A streptococci. However, that mere duration of the contact between antigen and host tissue is not the causative factor of the degree of antibody response is demonstrated by the fact that in the case of individual patients with scarlet fever tested at both three- and six-week intervals after the onset of the disease, no increase has been observed but, rather, a decrease of antibody content has occurred.[17]

The results of our survey indicate that close relationships exist between the degree of acute phase response and the antibody titer to group A streptococci. Also, these results provide a means of explanation for the demonstrated failure of a number of patients with proved uncomplicated streptococcal infection to develop antibody to the extracellular streptococcal antigens. The observed relative decrease of ASO and ASK titers concomitant with the presence of C-RP in the serum may explicate the frequently observed occurrence of normal ASO and ASK titers in the early stages of the acute rheumatic fever. Although no definite conclusions were obtained on the significance of C-RP and on its correlation with the chain of events that lead to antibody formation, the results presented in this study offer the possibility of a better evaluation of the significance of the C-RP and of ASO and ASK titers.

SUMMARY

The correlations between the early appearance of C-reactive protein in the serum and the subsequent production of antistreptolysin O and antistreptokinase antibodies were studied in fifty-seven patients with exudative pharyngitis produced by group A beta hemolytic streptococci, type 14. Only the patients who showed an early response to the streptococcal infection by the production of the abnormal C-RP later developed significant levels of ASO and ASK. A roughly quantitative correlation between the amount of C-RP appearing in the serum in response to streptococcal infection and the subsequent rise in antibody titers seemed apparent. No rise of ASO and ASK titers was evident in young patients who did not produce detectable amounts of C-RP during the acute phase of the streptococcal pharyngitis.

The correlations between the ASO and ASK titers and the amount of C-RP present in the serum were also studied in forty-six patients with acute rheumatic fever. Immunologic evidences of antecedent streptococcal infection were found in all the patients studied. The appearance of varying amounts of C-RP in the serum was concomitant to a relative decrease of the antibody titer during the "acute phase response." Furthermore, a relationship was evident between the amounts of C-RP present in the serum at the onset of the acute rheumatic fever and the subsequent rise of ASO and ASK titers.

REFERENCES

1. Stetson, C. A.: The Relation of Antibody Response to Rheumatic Fever; Streptococcal Infection, McCarty, M. (Ed.), New York, 1954, Columbia University Press, p. 208.
2. Rantz, L. A., Moroney, M., and DiCaprio, J. M.: Antistreptolysin O Response Following Hemolytic Streptococcus Infection in Early Childhood, Arch. Int. Med. **87**: 360, 1951.
3. Wood, H. F., and McCarty, M.: Laboratory Aids in the Diagnosis of Rheumatic Fever and in Evaluation of Disease Activity, Am. J. Med. **17**: 768, 1954.
4. Wood, H.: The Relationship Between the Acute Phase Response and Antibody Production in the Rabbit. I. Correlation Between the Early Appearance of C-Reactive Protein and the Subsequent Antibody Production, J. Exper. Med. **98**: 311, 1953.
5. Anderson, H. C., and McCarty, M.: Determination of C-Reactive Protein in the Blood as a Measure of the Activity of the Disease Process in Acute Rheumatic Fever, Am. J. Med. **8**: 445, 1950.
6. Swift, H. F., Wilson, A. T., and Lancefield, R. C.: Typing Group A Streptococci by M Precipitation Reaction in Capillary Pipettes, J. Exper. Med. **78**: 127, 1943.
7. Rantz, A. L., and Randall, E. A.: Modification of the Technic for Determination of Antistreptolysin Titer, Proc. Soc. Exper. Biol. & Med. **59**: 22, 1945.
8. Todd, E. W.: Antigenic Streptococcal Hemolysin, J. Exper. Med. **55**: 267, 1932.
9. Christensen, L. R.: Methods for Measuring the Activity of Components of the Streptococcal Fibrinolytic System and Streptococcal Desoxyribonuclease, J. Clin. Invest. **28**: 163, 1949.
10. Goldin, M., and Kaplan, M. A.: A Method for Obtaining Blood for Micro-Tests; Application to Determination of C-Reactive Protein and Antistreptolysin O Titers, Am. J. Clin. Path. **25**: 1432, 1955.
11. Libretti, A., Kaplan, M. A., and Goldin, M.: Precipitin Analysis of C-Reactive Protein by Gel Diffusion, Proc. Soc. Exper. Biol. & Med. **90**: 481, 1955.
12. Jones, T. D.: The Diagnosis of Rheumatic Fever, J. A. M. A. **126**: 481, 1944.
13. Commission on Acute Respiratory Diseases: Studies on Streptococcal Fibrinolysis. V. The in Vitro Production of Fibrinolysin by Various Groups and Types of Beta Hemolytic Streptococci; Relationship to Antifibrinolysin Production, J. Exper. Med. **85**: 441, 1947.
14. Wood, H.: The Relationship Between the Acute Phase Response and Antibody Production in the Rabbit. II. The Stimulation of C-Reactive Protein Response by Certain Adjuvants and the Relation of This Response to the Enhancement of Antibody Formation, J. Exper. Med. **98**: 321, 1953.
15. Kabat, E. A., Wolf, A., and Bezer, A. E.: Effect of Cortisone on Experimental Acute Disseminated Encephalomyelitis, Tr. Am. Neurol. A. **76**: 128, 1951.
16. Catanzaro, F. J., Brock, L., Chamovitz, R., Ferry, W. D., Siegel, A. C., Stetson, C. A., Rammelkamp, C. H., Jr., Houser, H. B., Stolzer, B. L., Wannamaker, L. W., and Hahn, E. O.: Effect of Oxytetracycline Therapy of Streptococcal Sore Throat on the Incidence of Acute Rheumatic Fever, Ann. Int. Med. **42**: 345, 1955.
17. Harris, T. N., Harris, S., and Ogburn, C. A.: Gel Precipitation of Streptococcal Culture Supernates With Sera of Patients With Rheumatic Fever and Streptococcal Infection, Proc. Soc. Exper. Biol. & Med. **90**: 39, 1955.

EXPERIMENTAL ARTERIAL SENSITIZATION

Studies on the Specificity of "Shock Tissue"

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INTRODUCTION

ALTHOUGH the exact mechanism of action of physiologic, immunologic, and biochemical factors in anaphylaxis has not definitely been established, the anatomic site of the reaction is a constant occurrence predictable for the individual species under study. Thus, the symptomatology of reactions of hypersensitivity is clearly a species variation dependent upon the phenomenon of the specificity of the participating "shock organ." In the guinea pig, this reaction occurs within the bronchioles; in the dog, it occurs in the hepatic veins within the liver; and in the rabbit, the pulmonary artery is involved.

Previous studies[1-4] have suggested that the occurrence of experimentally produced lesions of pulmonary vasculitis in the rabbit actually may be a function of the specificity of this tissue participating in immunologic reactions as a "shock organ." In these studies, utilization of the technique of passive sensitization and subsequent challenge in rabbits has demonstrated the uniform occurrence of panarteritis and perivascular lesions involving the arterioles and venules resulting from the in vivo antigen-antibody reaction. However, the reason for the localization of these lesions being limited to the pulmonary vasculature is not clearly understood. Hawn[5] has observed identical lesions in rabbits subjected to single large injections of bovine serum albumin and bovine serum gamma globulin.[6] The prerequisites for and the circumstances surrounding the production of these lesions, discussed elsewhere,[1-3] suggest that these lesions represent tissue manifestations of subacute anaphylaxis without any distinctive characteristics of the tissue response related to the particular antigen-antibody system involved. Thus, localization in a shock organ could explain the site of occurrence of a lesion resulting from an anaphylactic response of any degree of severity or duration of action.

However, the question of the importance of the role of the particular route of administration of the antibody and antigen in passive sensitization and challenge experiments must be justifiably considered. The manner of injection could influence the site and character of the resultant tissue alterations so that the intravenous route employed in these studies may predispose

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to the localization in pulmonary vessels since the lung is the first organ to receive uniform distribution of intravascular coursing antibody and antigen after their introduction through the ear vein. This problem of selective localization has been further considered and investigated here. By varying the routes of administration of antibody and antigen in the rabbit, certain internal organs, namely, the heart and lungs by the intravenous route, the brain through the intracarotid artery, and the liver by the intraperitoneal route, could be initially exposed to these immunologic factors before their further dilution in the blood stream, distribution to other organs, tissue fixation, or other dissipating factors could take place.

This report is concerned with a study and evaluation of the comparative involvement of the vasculature and the occurrence of vasculitis within these organs after each of these experimental procedures.

EXPERIMENTAL PROCEDURE AND RESULTS

The details of the procedure for the production of vascular lesions by passive sensitization in the rabbit, with a description of the lesions produced, are discussed in detail elsewhere.[1] Briefly, this consists of the administration of 5 ml. of high titer homologous rabbit antihorse serum into the marginal ear vein of a rabbit. After a half-hour incubation period allowing for circulation, distribution, etc., of the antibodies, the animal is challenged with the intravenous administration of horse serum diluted 1:100 in successive doses of 1 ml., 2 ml., 3 ml., 4 ml., and 5 ml. given at fifteen-minute intervals. Twenty-four hours later the animals are sacrificed by air embolism and sections of internal organs are taken for study.

Three series of New Zealand strain male albino rabbits, ranging in weight from 1,500 to 2,000 grams, were sensitized with rabbit antihorse serum with an antibody precipitin titer of 1:1,280, determined by titrations of antiserum dilutions against horse serum diluted 1:10,000. Variations in the route of administration and the doses of the passively sensitizing antiserum and subsequent challenging horse serum 1:100 were made as follows:

1. *Intravenous method:* These rabbits were passively sensitized with 5 ml. homologous antihorse serum and subsequently challenged with 15 ml. horse serum in divided doses, all injections being given through the ear veins according to the procedure described above.

2. *Intracarotid arterial method:* Sensitizing antiserum and challenging antigen injections were administered through the common carotid artery. In this series, the rabbits were lightly anesthetized with intravenous pentobarbital sodium. The common carotid artery was exposed and a 21 gauge cannula was inserted. This cannula was attached to a three-way stopcock and stay sutures were inserted. In this way, both satisfactory control of retrograde blood leakage and the administration of injections could be effected without disturbing the position of the cannula held in situ by ligatures. In order to allow for alternate circulation through the external carotid arterial system

and to insure that at least the prerequisite amounts of sensitizing antiserum and challenging antigen as required for the production of pulmonary vasculitis[1] would reach the brain directly through the internal carotid artery, double the dosages of antiserum and horse serum 1:100 employed in the intravenously administered series above were introduced into the common carotid cannula. Otherwise, the incubation period, time interval between doses, etc. were kept the same in both these series. Tissues from a group of three rabbits serving as a control for this series were studied in the same manner; these animals were sacrificed twenty-four hours after being subjected to exposure and ligation of a common carotid artery under pentobarbital sodium anesthesia.

3. *Intraperitoneal method:* In this series of rabbits, sensitizing antiserum and challenging antigen injections were administered intraperitoneally. Allowing for some alternate intraperitoneal absorption and drainage directly into the inferior vena caval system and in order to insure that at least the prerequisite amounts of sensitizing antiserum and challenging antigen as required for the production of pulmonary vasculitis[1] would reach the liver directly through the portal system, double the dosages of homologous antiserum and horse serum 1:100 employed in the intravenously administered series above were injected intraperitoneally. Otherwise, the incubation period, time interval between doses, etc. were kept the same as in the other series of animals.

TABLE I. NUMBER OF RABBITS DEVELOPING LESIONS OF PULMONARY VASCULITIS AFTER PASSIVE SENSITIZATION WITH HOMOLOGOUS ANTIHORSE SERUM AND CHALLENGE WITH HORSE SERUM UTILIZING THREE DIFFERENT ROUTES OF ADMINISTRATION

SENSITIZING AND CHALLENGING ROUTE	NUMBER OF ANIMALS	DEVELOPMENT OF LESIONS		
		NUMBER OF ANIMALS	RELATIVE DEGREE OF INTENSITY	RELATIVE FREQUENCY OF OCCURRENCE
Intravenous (ear vein)	10	10	+++-++++	Frequent
Intra-arterial (carotid)	9	3	0	Infrequent
		2	++	
		4	+++	
Intraperitoneal	8	5	0	Rare
		3	?+	

The degree of development of lesions is represented as follows: ++++, severe; +++, moderate; ++, mild; +, equivocal; 0, negative. In all animals no lesions were found in the heart, brain and liver.

Hematoxylin and eosin-stained sections of lung, heart, brain, and liver of all the animals subjected to the experimental procedures just described were studied microscopically. These results are summarized in Table I.

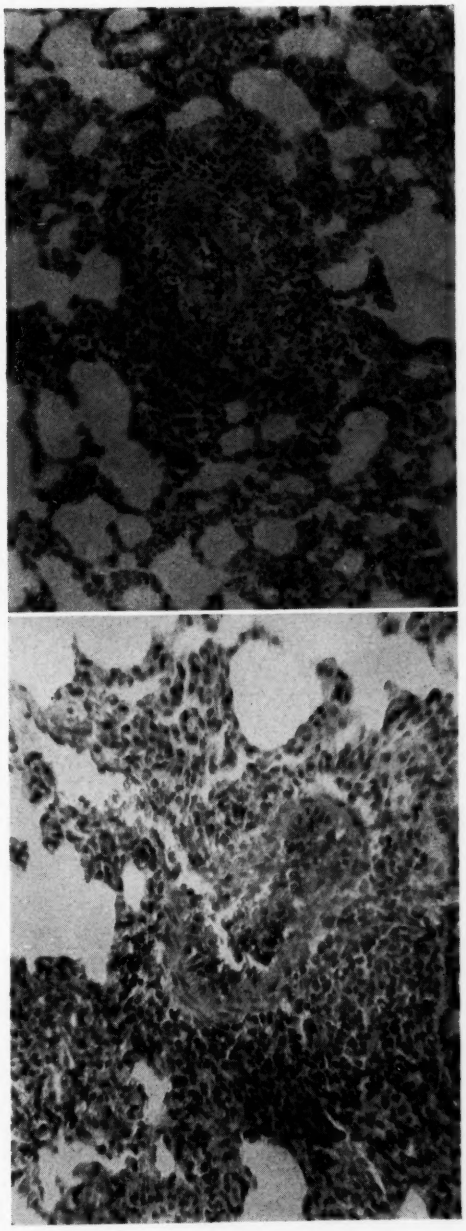
1. *Sensitization and Challenge Via the Ear Veins.*—All ten animals in this series exhibited the typical pulmonary vasculature lesions described in detail elsewhere.[1] The smaller pulmonary arteries, pulmonary arterioles, and venules showed (Fig. 1, *A*, *B* and *C*) marked perivascular and adventitial infiltration

A. *B.* *C.*

(Fig. 1, D and E on opposite page.)

Fig. 1.—Sections from lungs that had been passively sensitized with homologous anti-horse serum and subsequently challenged with subanaphylactic doses of horse serum through the ear veins (*A*, *B*, and *C*) and through the carotid arteries (*D* and *E*). These show perivascular infiltrations with polymorphonuclear leukocytes and eosinophilic granulocytes. There are a few eosinophils seen infiltrating the adventitia, media, and intima of the pulmonary arterioles (*B*, *D*, and *E*) and *B*, *C*, and *D* show some intimal proliferation. Intraluminal accumulations of eosinophilic granulocytes and polymorphonuclear leukocytes are seen in *B*, *C*, *D*, and *E*.

D.



E.

Fig. 1.—*D* and *E*. *(For legend, see opposite page.)*

of eosinophilic granular-staining leukocytes, polymorphonuclear neutrophilic leukocytes and, to a much lesser extent, a few lymphocytes and mononuclear cells. Eosinophils were found infiltrating the intima and media of the arteries

and in several instances collections of eosinophils and a few polymorphonuclear leukocytes were found within the lumina of these vessels. In several sections, varying degrees of hyperplasia of the endothelial cells of the intima, early thrombus formation, cloudy swelling of the muscle fibers with hydropic degeneration of the media, and some adventitial edema were found. On a comparative basis, the average intensity of these vascular lesions was considered to be moderately severe (+++ – ++++). In all these sensitized animals, the heart, liver, spleen, kidneys, pancreas, adrenals, and brain were microscopically negative for similar lesions of vasculitis.

2. *Sensitization and Challenge Via Intracarotid Arterial Route.*—Nine rabbits survived this procedure without developing any apparent symptoms or complicating pathologic processes, such as pneumonia. The lungs of three of these animals either failed to show any evidence of the development of vasculitis or such lesions were equivocal (+). The other six exhibited lesions of pulmonary vasculitis (Fig. 1, *D* and *E*), two of a mild degree of development (++), and four of moderate intensity (+++). These lesions presented the same qualitative microscopic picture as described in Series 1 (intravenous sensitization and challenge), but were generally less evident and somewhat less severe in nature. The same perivascular infiltrate of eosinophilic granular-staining leukocytes and polymorphonuclear leukocytes was noted, but this was often lighter in degree. Eosinophilic leukocytes were again seen penetrating the arterial coats and intimal proliferation, intraluminal cellular accumulations, and early thrombus formation occasionally were observed. In no instance were any lesions of as severe a degree noted as were often observed in the lungs of those animals sensitized and challenged by the ear vein (Series 1). Multiple serial sections through the brain revealed no evidence of microscopic lesions of vasculitis in the white and gray matter or in the meningeal vessels. The heart and liver likewise were microscopically negative.

3. *Sensitization and Challenge Via the Intraperitoneal Route.*—Of eight rabbits subjected to this procedure, the lungs of five were microscopically negative and the remaining three exhibited the occasional occurrence of only questionable or equivocal pulmonary vascular lesions of a mild degree (+). Multiple microscopic sections through the liver failed to reveal the presence of any vascular lesions in the hepatic parenchyma, and studies of the heart and brain likewise demonstrated no microscopic abnormalities.

In the brains of one or two rabbits from each series, there were observed vascular lesions characterized by perivascular infiltration of mononuclear cells into the Virchow-Robin spaces of the cerebral vasculature. These lesions, however, probably were due to a complicating protozoan endemic parasitic infection of rabbits, *Encephalitozoon cuniculi*, rather than to any of the sensitizing procedures employed. Although these lesions might possibly be confused with those of a hypersensitivity vasculitis, it is noteworthy that their characteristic infiltrate of mononuclear cells represents a much more chronic process

than could be expected to develop within a twenty-four-hour period following sensitization, polymorphonuclear leukocytes and eosinophilic cells being more characteristic of an acute response in this later process.*

DISCUSSION

By modifying a previously described technique for the production of pulmonary vasculitis,[1] a by-passing of the lung was attempted so that other internal organs could be initially exposed to antibody and antigen under the same conditions found favorable for producing these lesions of the pulmonary vasculature. Thus, as the intravenous route will initially supply the immunologic reactants to the heart and lungs, these reactants were first made available to the brain via the intracarotid arterial route and to the liver by intraperitoneal injections. It was anticipated that the results of this study might contribute information regarding such unestablished points as whether the pulmonary vasculature possesses some particular distinctive characteristic allowing it, as a specialized tissue ("shock organ"), to participate in subacute anaphylactic reactions, or whether other organs, such as brain and liver, under similar experimental conditions behave in a similar resultant fashion.

The microscopic study of these organs seems to indicate that the frequency and intensity of involvement of the pulmonary arteries, arterioles, and venules may well depend upon the administration of the passively sensitizing factors through the ear vein. Because of their segmental nature and irregular distribution, it is extremely difficult to quantitate these lesions. By the examination of multiple lung sections, however, the impression is gained that these lesions occurred most frequently when antibody and antigen were administered by the intravenous route, infrequently by the intracarotid arterial route, and rarely when the intraperitoneal route was employed. This also paralleled the similar relationship noted between the degree of intensity of the individual lesions and the route of administration. The greater the opportunity for the reduction of amount or concentration of antibody and antigen presented to the pulmonary vasculature, the lesser the extent and degree of development of lesions of vasculitis appears to have occurred. The mechanism is not apparent, but it could have been accomplished through such means as a dilution factor within the blood stream or an actual loss of antibody and antigen by virtue of diffusion, filtration, tissue fixation, or their interaction and inactivation within other organs before reaching the pulmonary vascular bed.

Lesions of vasculitis similar to those occurring within the lung could not be found in other internal organs exposed to antibody and antigen under similar conditions. Consideration was given to the possible escape of an undetermined percentage of antibody and antigen through alternate routes other than the portal system after intraperitoneal absorption and to extracerebral routes through the external carotid branches after introduction into the common carotid artery. Therefore, in order to insure that previously

*The authors wish to acknowledge with appreciation the assistance of Dr. Abner Wolf, Department of Pathology, Columbia University College of Physicians and Surgeons, in the evaluation of these lesions.

determined prerequisite amounts of sensitizing antiserum and challenging antigen would reach the liver and brain, compensating increased dosages were given when these two routes were employed. Although endocarditis and valvulitis were not observed in the right auricle or ventricle, even though these cardiac chambers received antibody and antigen before the pulmonary vascular bed, it is to be noted that the cardiac musculature could not be exposed to these immunologic agents via the coronary arteries without their preliminary circulation through and possible removal by the lung. Therefore, the absence of myocarditis and coronary arteritis is not considered significant in these intravenous passive sensitization experiments.

Although lesions of vasculitis were not found within the brain or liver, there is no proof that antigen or antibody was not removed by these organs or that their actual in vivo interreaction did not occur within these sites without the resultant production of vasculitis, perhaps due to some particular inability of hepatic or cerebral vessels to participate in or respond to the effect of an anaphylactic type antigen-antibody tissue reaction. A possible modifying effect of pentobarbital sodium also must be considered, since it has been noted that anesthesia may depress the degree of anaphylaxis, but this is only a relative effect for shock can be elicited by simply increasing the doses of antigen.[7]

It has long been observed that the intraperitoneal administration of challenging doses of antigen in sensitized animals attenuates anaphylactic shock. This has generally been attributed to a slower rate of absorption of the antigen into the blood stream delaying its arrival at the site of reaction. Actually, there is no proof that antigen and/or antibody is absorbed out of the peritoneal cavity. However, an actual removal of the foreign protein antigen by the liver must be considered in explaining the protective effect of the intraperitoneal sensitizing and challenging route not only on the more acute symptoms of anaphylactic shock, but also on the development of pulmonary vascular lesions. Whether the suppressive effect in this latter regard can be overcome by employing larger sensitizing and challenging doses is not apparent and is a matter for further study.

Lesions of vasculitis in internal organs other than the lung have been demonstrated in rabbits actively sensitized with large amounts of antigen. However, unlike passive sensitization and challenge procedures which are concerned only with the antigen-antibody reaction, these experimental techniques are associated with a number of uncontrolled factors that may influence the production of mesenchymal tissue reactions, such as foreign material disposition[8] and antibody production[9] and the appearance of vascular lesions whose character and distribution may depend on the chemical nature of the particular antigen employed[6] or are found associated with chemical and physical irritation.[10] The failure to find acute lesions of the type described in this study in organs other than the lungs by passive sensitization and challenge experiments can be interpreted only as evidence that the pulmonary vasculature, in contrast to that of the liver and brain, possesses some ill-understood specificity in participating in acute or subacute in vivo antigen-antibody reactions within the limits of the experimental conditions employed

in this study. There has been considerable evidence accumulated as reviewed by Stevenson and Alvord[11] and by Hurst,[12] which demonstrates that vascular lesions of the central nervous system in experimental animals can arise as a result of hypersensitivity and other immune mechanisms. Although some cerebral lesions possibly may arise as a result of simple anaphylactic shock,[13-15] those cerebral vascular lesions of hypersensitivity produced in the rabbit appear to be associated with or dependent upon different immunologic mechanisms, such as the local Arthus phenomenon,[16] organ-specific antibrain antibodies[17, 18] arising from injections of brain antigen as employed in the production of experimental encephalomyelitis in this species,[19-21] or the Forssman antibody reaction of the guinea pig[22, 23] where the antigen probably naturally occurs in the vascular endothelial cells or within the parenchyma of the central nervous system.[22]

Although the reason for the predilection of the vascular tissue response for the lung, especially as regards the frequency, extent, and intensity of lesions, has been shown to arise largely as a function of the route of administration of passively sensitizing antibody and challenging antigen, nevertheless, there does appear to be some specificity of the pulmonary vasculature in this process not residing in the endocardium, brain, or liver. Whether this may depend on selective localization of antigen and/or antibody or their interaction within the pulmonary vasculature or on some unusual sensitivity of this tissue in responding to this reaction is a matter only for speculation. Although not apparent, perhaps the reason may be found among those theories advanced to explain the specificity of the mode of action of the "shock organ" tissue in anaphylaxis. Comprehensive reviews and discussions [7, 24-29] of the evidence to explain this complex and incompletely understood reaction appear elsewhere and need not be discussed in detail here. However, some of the variations of these theories are worthy of mention in that any one or combination of these proposed mechanisms might explain the participation of selective tissues as specialized "shock organs."

1. Differences may be partly due to the anatomic differences in the quantitative distribution of maximally contracting smooth muscle in various organs.[7, 29]

2. Intrinsic differences may exist in the degree of sensitivity acquired by the organ in various species.[7] (This may include sensitivity to histamine or one of the other suspected released pharmacologically active agents, for example, adenosine derivatives, acetylcholine, potassium ions, proteoses, and peptones.[26]

3. Different biologically active substances are released from different tissues, depending on the chemical nature of the particular tissue, with the shock organ more susceptible to these increased substances.[30]

4. Abell and Schneck[31] have demonstrated that during anaphylactic shock in the rabbit, the leukocytes become sticky and adhere in clumps to the vascular endothelium in the finer pulmonary vessels.

This trapping, redistribution, and possible sequestration[32] of leukocytes of a high histamine content[33] within the pulmonary bed might lead to the selective exposure of histamine to the pulmonary circuit.[25]

5. Increased histamine in the pulmonary circulation and, as suggested by Feldberg,[34] the main release of histamine may occur in juxtaposition to the pulmonary arteries.

6. The physical theory[7, 35] of anaphylaxis holds that the toxic stimulus or interference with normal physiology results from physical changes at the surface or within the protoplasm of tissue cells following antigen-antibody union. (The "shock organs" may be those whose tissue cells are most affected.)

7. Dixon,[36] utilizing radioactive tagged antigen, has demonstrated the appearance of a precipitated-like material within the pulmonary blood vessels following anaphylactic shock. The tortuosity of the capillaries of the lung and the size of the pulmonary vascular bed thus might be important in trapping or filtering out[37, 38] this precipitate, particulate matter or any resultant physical changes in the colloidal dispersion of antigenic substances or antibody globulin[27] which may be affected by antigen-antibody reactions as suggested by the physical theory.[7, 35]

8. Halpern and associates[39] suggest that the localization and elective choice of the shock organ may depend upon the fixation of antibodies in high titer in a region that has been predisposed by exposure to traumatic factors and local liberation of histamine. Whether or not the lesions of pulmonary vasculitis can be proved to be a tissue manifestation of subacute anaphylaxis can be determined only if both this tissue reaction and that of anaphylactic shock are found to possess a common denominator in one or more of the above-mentioned immunologic, biochemical, or physiologic mechanisms or perhaps mediated through some yet undetermined mode of action.

SUMMARY

1. Albino rabbits of the same strain and approximate age and weight were passively sensitized with homologous antiserum to and challenged with horse serum according to a procedure favoring the production of acute lesions of vasculitis of the pulmonary arteries, arterioles, and veins.

2. Of ten animals sensitized and challenged intravenously through the ear vein, all developed the typical lesions of periarterial infiltration consisting chiefly of eosinophils and polymorphonuclear leukocytes and, to a much lesser extent, lymphocytes and mononuclear cells with some eosinophilic infiltration into the adventitia, media, and intima of the small pulmonary arteries and arterioles. The vasculature of other organs was unaffected.

3. Of nine animals subjected to similar procedures via the intracarotid arterial route, six developed similar pulmonary lesions, but the lesions were of

milder intensity and were less frequently found than those sensitized and challenged by the intravenous route. The brains of these rabbits were free of lesions.

4. Eight animals received similar sensitizing and challenging injections intraperitoneally. In this group, lesions suggesting pulmonary vasculitis were infrequently found and were of a very mild or equivocal degree. Lesions could not be demonstrated within the liver following this procedure.

5. These results suggest that although modified by the route of administration of sensitizing and challenging doses, the development of acute lesions of pulmonary vasculitis may depend upon some undetermined specificity of the rabbit lung in participating in antigen-antibody reactions not found in the brain or liver of this animal.

6. Although not apparent, the reason for the involvement of the pulmonary vasculature in this reaction, considered a tissue manifestation of subacute anaphylaxis, may be related to the role of the pulmonary arteries as "shock organ" in anaphylactic shock.

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REFERENCES

1. Cohen, S. G., Mayer, L. D., and Criep, L. H.: The Experimental Production of Arteritis by Passive Sensitization, J. Immunol. **66**: 487, 1951.
2. Cohen, S. G., and Moses, C.: Effect of Cortisone on Experimental Production of Arteritis by Passive Sensitization, J. Lab. & Clin. Med. **37**: 764, 1951.
3. Cohen, S. G., Mokychic, W. E., and Drapiewski, J. F.: The Etiological Role of Streptococcus Toxin-Antitoxin Systems in the Experimental Production of Arterial Sensitization, J. ALLERGY **24**: 411, 1953.
4. Cohen, S. G., Walsh, J. W., and Dzury, D. S.: The Effect of Biologic and Chemical Agents on the Experimental Production of Arteritis by Passive Sensitization. II. Nitrogen Mustard, J. Immunol. **73**: 100, 1954.
5. Hawn, C. V. Z.: Personal Communication.
6. Hawn, C. V. Z., and Janeway, C. A.: Histological and Serological Sequences in Experimental Hypersensitivity, J. Exper. Med. **85**: 571, 1947.
7. Boyd, W. C.: Fundamentals of Immunology, ed. 2, New York, 1947, Interscience Publishers, Inc., pp. 307-321.
8. Ehrich, W. E.: The Significance of Tissue Reactions Caused by Antigens, J. A. M. A. **135**: 94, 1947.
9. Erich, W. E., Seifter, J., and Forman, C.: Experimental Serum Disease, A Pathogenic Study, J. Exper. Med. **89**: 23, 1949.
10. Klemperer, P.: Diseases of the Collagen System, Bull. New York Acad. Med. **23**: 581, 1947.
11. Stevenson, L. D., and Alvord, E. C., Jr.: Allergy in the Nervous System; A Review of the Literature, Am. J. Med. **3**: 614, 1947.
12. Hurst, E. W.: Experimental Demyelination in Relation to Human and Animal Disease, Am. J. Med. **12**: 547, 1952.
13. Weinberg, E.: Histologische Veränderungen in Gehirn Während des Anaphylaktischen Schocks, Ztschr., ges. Neurol. u. Psychiat. **87**: 451, 1923.
14. Steif, A., and Tokay, L.: Durch Experimentelle Serumanaphylaxie Veränderungen des Nerven Systems, Ztschr. ges. Neurol. u. Psychiat. **150**: 715, 1934.
15. Baginski, S., Czarnecki, E., and Hurynoincz, J.: Lesions histologiques du Système Nerveux des Lapins en État Anaphylactique, Compt. rend. Soc. biol. **130**: 567, 1939.
16. Davidoff, L. M., Seegal, B. C., and Seegal, D.: The Arthus Phenomenon: Local Anaphylactic Inflammation in the Rabbit Brain, J. Exper. Med. **55**: 163, 1932.
17. Lewis, J. H.: The Immunologic Specificity of Brain Tissue, J. Immunol. **24**: 193, 1933.
18. Schwentker, F., and Rivers, T. M.: The Antibody Response of Rabbits to Injections of Emulsions and Extracts of Homologous Brain, J. Exper. Med. **60**: 559, 1934.
19. Morrison, L. R.: Disseminated Encephalomyelitis Experimentally Produced by the Use of Homologous Antigen. Arch. Neurol. & Psychiat. **58**: 391, 1947.

20. Kopeloff, L. M., and Kopeloff, N.: Neurologic Manifestations in Laboratory Animals Produced by Organ (Adjuvant) Emulsions, J. Immunol. **57**: 179, 1947.
21. Waksman, B. H., Porter, H., Lees, M. D., Adams, R. D., and Folch, J.: A Study of the Chemical Nature of Components of Bovine White Matter Effective in Producing Allergic Encephalomyelitis in the Rabbit, J. Exper. Med. **100**: 451, 1954.
22. Jervis, G. A.: Forssman's "Carotid Syndrome," A Contribution to the Study of Anaphylactic Changes in the Nervous System From the Standpoint of Pathology, Arch. Path. **35**: 560, 1943.
23. Arbesman, C. E., Terplan, K. L., Neter, E., and Bertram, L. F.: The Effects of ACTH and Cortisone on the Pathology of Reversed Anaphylaxis in the Guinea Pig, J. ALLERGY **26**: 123, 1955.
24. Ratner, B.: Allergy, Anaphylaxis and Immunotherapy, Baltimore, 1943, Williams & Wilkins Company, pp. 599-626.
25. Dragstedt, C. A.: The Significance of Histamine in Anaphylaxis, J. ALLERGY **16**: 69, 1945.
26. Chase, M. W., in Dubos, R. J., ed.: Bacterial and Mycotic Infections of Man, ed. 2, Philadelphia, 1952, J. B. Lippincott Company, pp. 171-183.
27. Sherwood, N. P.: Immunology, ed. 3, St. Louis, 1951, The C. V. Mosby Company, pp. 551-586.
28. Raffel, S.: Immunity, Hypersensitivity, Serology, New York, 1953, Appleton-Century-Crofts, Inc., pp. 207-214.
29. Seegal, B. C.: Experimental Anaphylaxis in Lower Animals, Ann. New York Acad. Sc. **50**: 681, 1949.
30. Wents, cited by Boyd,[7] p. 320.
31. Abell, R. G., and Schneck, H. P.: Microscopic Observations on the Behavior of Living Blood Vessels of the Rabbit During the Reaction of Anaphylaxis, J. Immunol. **34**: 195, 1938.
32. Katz, G.: Histamine Release From Blood Cells in Anaphylaxis in Vitro, Science **91**: 221, 1940.
33. Code, C. F.: The Source of Blood in the Histamine-Like Constituent, J. Physiol. **90**: 349, 1937.
34. Feldberg, W.: Histamine and Anaphylaxis, Ann. Rev. Physiol. **3**: 671, 1941.
35. (A) Weil, R., (B) Doerr, R., (C) Opie, E. L.: Cited by Sherwood,[27] p. 574.
36. Dixon, F. J.: The Use of I^{131} in Immunologic Investigation, J. ALLERGY **24**: 547, 1953.
37. Brickner, R. M.: Role of the Capillaries and Their Endothelium in the Distribution of Colloidal Carbon by the Blood Stream, Bull. Johns Hopkins Hosp. **40**: 90, 1927.
38. Rich, A. R.: The Pathogenesis of Tuberculosis, ed. 2, Springfield, Ill., 1951, Charles C Thomas, p. 317.
39. Halpern, B. N., Biozzi, G., and Benacerraf, B.: Mise en evidence du rôle des facteurs irritatifs et des traumatismes dans la localisation éléctive des anticorps dans les organes de choc, Acta. allergol. **8**: 181, 1955.

THE USE OF PREDNISOLONE (STERANE) IN THE TREATMENT OF SEVERE ALLERGIC DISEASES

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THE purpose of this presentation is to relate our experiences with the short-term use of prednisolone (Sterane) in the treatment of some severe allergic conditions. Two hundred thirty-two courses of Sterane were given to 201 patients for the conditions shown in Table I. We list two cases of psoriasis and one of metastatic carcinoma of the prostate in which the drug was given because of intense pruritus not relieved by other measures.

DOSAGE

The usual dosage was planned to be 150 mg. taken over a twelve-day period, starting with 20 mg. daily and reducing the dose gradually. While this was an average schedule, we soon found that it was better to vary it with different conditions and with different patients.

SEVERE RAGWEED HAY FEVER

Twenty-four patients who were refractory to conventional treatment were given twenty-five courses of Sterane. There were twelve male patients and twelve female patients, and their ages ranged from 14 to 60 years. Results were judged to be excellent in twenty cases, good in three, and poor in one. The response usually was dramatic, with marked improvement occurring within twenty-four hours. This effect was too regular to be coincidental. Several patients had recurrences of symptoms after marked reduction of the dose or cessation of treatment, but were responsive to conventional therapy. In one case, a short course of Sterane was repeated.

We found Sterane to be a useful and effective drug in these refractory cases. Three patients had had previous cortisone therapy, and all considered Sterane much more effective. The one patient who had poor results was the only one of the series who had had no specific injection treatment.

BRONCHIAL ASTHMA

Eighty-five patients with intractable asthma were treated with prednisolone. The plan was to give short courses or interrupted therapy. We found, however, that ten patients with severe emphysema invariably became more

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Sterane and counsel were generously supplied by Dr. M. William Amster, Director of Medical Service of Pfizer Laboratories, Brooklyn, New York.

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dyspneic as soon as the daily dose was decreased below a certain point, so that small maintenance doses were necessary. This dose is usually in the amount of 10 mg. daily, more or less. With a few exceptions, infection was thought to be a causative factor in the intractable cases, so that antibiotic therapy the first few days was almost routine.

It has been our very definite impression that prednisolone is more effective and prompt in its effect than either cortisone or hydrocortisone. Patients who had taken prednisone were so few that we could make no valid comparison of the two drugs. Certainly the lack of need for salt restriction is evident, and for this both we and the patients are grateful.

TABLE I. STERANE (PREDNISOLONE) IN THE TREATMENT OF SEVERE ALLERGIC DISEASES*

DIAGNOSIS		NUMBER OF CASES
Bronchial asthma		85
Ragweed hay fever		25
Contact dermatitis		25
Atopic dermatitis		17
Nummular eczema		11
Perennial allergic rhinitis		11
Rhinitis medicamentosa		7
Miscellaneous		21
Urticaria and angio-edema	4	
Exfoliative dermatitis	3	
Drug eruption (arsenic, mercury, digitalis)	3	
Intractable pruritus from cancer of prostate	1	
Serum sickness (penicillin and anti-snake venom)	2	
Intractable pruritus ani	1	
"Id" reaction from penicillin	1	
Psoriasis	2	

*Two hundred thirty-two courses administered to 201 patients.

Side reactions were few. In only two of eighty-five patients was it necessary to stop the drug—in one because of abdominal pain, in the other because of vomiting.

CONTACT DERMATITIS

Twenty-five cases of severe contact dermatitis were treated. An average of 160 mg. was given in an eight-day period, the day-to-day dose being reduced as improvement became evident. Prednisolone was very effective in relieving itching in the majority of cases. Objective improvement was decidedly more prompt and evident than could have been expected from the usual wet packs, lotions, and creams, which were also used.

ATOPIC DERMATITIS

Our experience with seventeen cases of atopic dermatitis does not make us too optimistic. Of these, six were adults, eight were children, and three were infants. It is true that relatively large doses usually reduced inflammation and pruritus. Symptoms became exacerbated, however, as soon as the dose was reduced to 15 mg. daily in the adult type. One adult female patient showed no improvement on relatively large doses and became much worse after discontinuation. "Addiction" seemingly would be high, particularly

in those adult forms not helped by other therapy. In our opinion, corticosteroid therapy is strictly an emergency or last resort measure in older children and adults with atopic dermatitis.

NUMMULAR ECZEMA

Oral prednisolone did not seem worth while in treating eleven cases of nummular eczema. It is our opinion that the drug could have been expended more profitably if used locally in this condition.

PERENNIAL ATOPIC RHINITIS

Eighteen cases were treated with oral prednisolone. All were refractory to other forms of therapy. Seven were confirmed nose drop addicts. All were able to discontinue their nose drops following oral prednisolone therapy. The response was predictably dramatic. Reduction in daily dose was usually started within the first twenty-four hours. The dose was reduced rapidly and conventional measures sufficed after a very few days.

TABLE II. SIDE REACTIONS (OR COINCIDENTAL REACTIONS) IN 232 COURSES OF STERANE (PREDNISOLONE)

A. *Gastrointestinal*—25	
	Gas and nausea—12
	Vomiting—1
	Abdominal pain—3
	Constipation—3
	Flare-up of ulcer—2
	Increased appetite—4
B. *Central Nervous System Symptoms*—10	
	Insomnia—4
	Nervousness—3
	Headaches—2
	Bed-wetting—1
C. *Miscellaneous*—7	
	Five pounds or more weight gained—1
	Acneform eruption—1
	Swelling of mouth and tongue—1
	Severe impetigo developing under therapy—1
	Acute maxillary sinusitis developing under therapy—1
	Pneumonia developing under therapy—2

SIDE REACTIONS

Patients were not warned of any specific side reaction. In listing them (Table II), no distinction was made between expected symptoms and those which might be coincidental. There were twenty-five instances of gastrointestinal symptoms, with one case of vomiting and three of actual pain. One patient was hospitalized because of the severity of the pain. No ulcer was found. Three of the patients had a definite history of ulcer. Two of these are included in those with more severe symptoms above. One, however, had no side reactions of any kind.

Infections which occurred while under therapy probably are significant. There were one case of acute maxillary sinusitis, one of severe impetigo, and two of pneumonia. All responded favorably to antibiotic therapy.

OVER-ALL RESULTS

The results, as in any therapeutic procedure, are difficult to evaluate. We have used the best subjective and objective means at our disposal. It is impossible to put the results on an accurate percentage basis. These were obviously so good in all allergic conditions except nummular eczema and atopic dermatitis that we know that we have a very useful drug in prednisolone. We withhold any judgment concerning its oral use in atopic dermatitis and nummular eczema. We were particularly surprised at the immediate and complete relief given to a patient with metastatic carcinoma of the prostate, who had lain for days complaining bitterly of intense general pruritus. There were no skin lesions to account for this.

SUMMARY

We have found prednisolone to be a very effective, convenient, and safe form of corticosteroid therapy. Severe side reactions were not numerous. These subsided quickly with cessation of the drug. It is still our opinion that such medications should be reserved for emergencies, such as symptoms of unusual severity, and intractability to other forms of treatment. Our experience is largely limited to short-term therapy. The ten patients who are being maintained on small doses of prednisolone all have intrinsic asthma with advanced emphysema. It has been impossible in these to interrupt therapy without severe exacerbation of symptoms.

Our experience supports the general opinion that peptic ulcer and certain infections are contraindications to its use.

Prednisolone is our drug of choice in severe drug reactions (except anaphylaxis requiring epinephrine), acute pollinosis, severe contact dermatitis, and severe urticaria with angioedema. We feel that it shares honors with ACTH in the treatment of intractable asthma.

Erratum

In the July issue of THE JOURNAL OF ALLERGY, in the article by Cooke et al. entitled "Spontaneous and Induced Allergies of the Immediate Wheal Type in Man," on page 325, second last line of the first paragraph, the word "ovary" should have been capitalized, referring to the article by Ovary and Biozzi. This is also true in Table II, under P.C.A.

Reference: Ovary, Z., and Biozzi, G.: Passive Sensitization of the Skin of the Guinea Pig With Human Antibody, Internat. Arch. Allergy **5**: 241, 1954.

AN EVALUATION OF THE TREATMENT OF 259 CASES OF INFLAMMATORY DERMATOSES WITH HYDROCORTISONE FREE ALCOHOL OINTMENT

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THE value of hydrocortisone when used topically for certain inflammatory dermatoses has now become well established.[1-3] Moreover, it recently has been shown that the free alcohol of hydrocortisone appears to be more effective than hydrocortisone acetate when used locally.[4, 5] This study attempted to evaluate the results of topical treatment of some of the more common inflammatory dermatoses with hydrocortisone free alcohol ointment.

METHODS AND MATERIALS

Two hundred fifty-nine patients were treated with ointments containing hydrocortisone free alcohol in both a 2.5 per cent and a 1 per cent concentration. In most cases, treatment was instituted initially with the 2.5 per cent ointment and, after improvement was noted, the 1 per cent strength was used.

RESULTS

Table I summarizes the results of treatment in the 259 patients treated. Those patients showing marked subjective and objective improvement within a period of twenty-four hours or less were placed in the "excellent" group, while patients exhibiting moderate, though definite, improvement within twenty-four to forty-eight hours were put in the "good" category. Cases showing slight or no improvement were described as "poor." Some patients received only the 1 per cent hydrocortisone free alcohol ointment; the majority, however, were given the 2.5 per cent strength first and later, after improvement was observed, the 1 per cent concentration. Almost without exception, such patients were able to maintain their improvement when using the weaker concentration.

The most dramatic results were obtained in the treatment of contact dermatitis, neurodermatitis, and pruritus ani et vulvae. The virtually immediate relief of intense itching literally amazed three patients who had experienced intractable neurodermatitis for periods in excess of twenty years. Marked subjective improvement was observed practically as soon as the ointment was applied in 90 per cent of all cases of contact dermatitis. One patient initially complained of extremely severe itching at scattered points over the body without exhibiting any evidence of an eruption. Her pruritus did not

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The hydrocortisone ointment used in this study was supplied as Cortril topical ointment through the courtesy of Chas. Pfizer & Co., Inc.

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TABLE I. RESULTS OF TREATMENT OF 259 CASES WITH HYDROCORTISONE FREE ALCOHOL OINTMENT

RESULTS	CHRONIC ECZEMA OF HANDS	POISON IVY DERMATITIS %	PRURITUS VULVAE AND/OR ANI	CHRONIC ALLERGIC (ATOPIC) ECZEMA	CONTACT DERMATITIS	NEURODERMATITIS	CHRONIC DISCOID LUPUS ERYTHEMATOSUS	PITYRIASIS ROSEA	HERPES ZOSTER	STASIS ECZEMA OF LOWER EXTREMITIES	HODGKIN'S DISEASE	LICHEN PLANUS	TOTALS
Strength of Ointment 2.5%													
Excellent	9	3	17	4	46	41				2			122
Good	9	3	3	5	15	22		1		1			59
Poor	4	1	3	1	3	6	3	1	1		1	1	25
Strength of Ointment 1%													
Excellent	3	2	1	1	13	10		1		1			32
Good	1	3	1	3	4	4		1					17
Poor					1	2		1					4
Totals	26	12	25	14	82	85	3	5	1	4	1	1	259

respond to hydrocortisone free alcohol ointment (2.5 per cent). Three weeks later she abruptly developed generalized adenopathy, and a lymph node biopsy revealed the diagnosis of Hodgkin's disease.

Clinically, no evidence of percutaneous absorption was noted. Six cases of chronic allergic (atopic) eczema had practically generalized involvement and the ointment was applied over extensive areas for as long as two months without any untoward effect.

SUMMARY AND CONCLUSION

Two hundred fifty-nine patients were treated with hydrocortisone free alcohol ointment in both the 2.5 per cent and 1 per cent concentrations. This drug, when used topically, was particularly useful in the treatment of contact dermatitis, neurodermatitis, and pruritus ani et vulvae; response to the ointment in these conditions often was spectacular. In most instances, maintenance therapy, wherever necessary, could be carried on with the weaker (1 per cent) concentration.

REFERENCES

1. Sulzberger, M. B., and Witten, V. H.: Hydrocortisone (Compound F) Acetate Ointment in Dermatological Therapy, J. A. M. A. **151**: 468, 1953.
2. Robinson, H. M., Jr., and Robinson, R. C. V.: Treatment of Dermatoses With Local Application of Hydrocortisone Acetate, J. A. M. A. **155**: 1213, 1954.
3. Frank, L., Stritzler, C., and Kaufman, J.: Hydrocortisone (Compound F) Free Alcohol and Hydrocortisone Acetate for Topical Use, A. M. A. Arch. Dermat. & Syph. **71**: 117, 1955.
4. Heilson, B., Kristjansen, A., and Reymann, F.: Hydrocortisone in Therapy of Cutaneous Disease, A. M. A. Arch. Dermat. & Syph. **70**: 360, 1954.
5. Sulzberger, M. B., Witten, V. H., and Smith, C. C.: Hydrocortisone (Compound F) Free Alcohol Ointment, Correspondence, J. A. M. A. **152**: 1456, 1953.

Editorial

ATOPIC DERMATITIS

LOUIS TUFT'S discussion of Baer's* book on atopic dermatitis, in the May issue of THE JOURNAL OF ALLERGY, is of considerable interest and most allergists probably will agree with his criticisms of it. There are two sides to the question, however.

The trouble with most dermatologists is that they do not see atopic dermatitis as one *part* of a disease process. They are not familiar with the other parts of the triad—hay fever and asthma—and they do not sufficiently realize that the techniques applicable to the treatment of hay fever and of asthma often may be used with profit in dealing with atopic dermatitis. They have become too easily discouraged because these techniques do not always work. They tend to magnify the foolish things that are sometimes done by allergists and to overlook the many worth-while things that they do.

In order to deal with atopic dermatitis, it is well to know intimately hay fever and asthma; the three are equally important parts of the same basic situation, and there are things about hay fever and asthma that throw considerable light on atopic dermatitis. If dermatologists knew more about these, they would do better with atopic dermatitis. They pay too little attention to the immunologic aspects of it.

A failing of many allergists is that they do not have the dermatologic point of view which is so necessary in dealing with any disorder of the skin, be it atopic dermatitis or what-have-you. Many of them have never practiced medicine except as it relates to allergy; their viewpoint is often too narrow. They have too much faith in the immunologic approach—in desensitizing inoculations, a very clumsy method of treatment which, to be sure, sometimes does a great deal of good but which all too often does no good whatever, whether the disease treated be hay fever, asthma, or atopic dermatitis. They are likely to do too many skin tests, and to rely too much on them, and when they concentrate so intensely on immunology, as they usually do, they sometimes ignore other factors which may be of more practical importance. It is certain that the immunologic approach is desirable in atopic dermatitis; possibly it may someday solve the problem. The trouble is that at present it too often does not work.

Every allergist who expects to treat atopic dermatitis should spend some time working in a dermatology clinic. Dermatology is a vital part of his business. He usually is not much of a dermatologist and, as a rule, he pays

*Atopic Dermatitis, Edited by Rudolph L. Baer (5 contributors), J. B. Lippincott Company, Philadelphia, 1955, 112 pp.

too little attention to local treatment or to any other treatment that does not have to do with antigen antibody reactions. He is too likely to be primarily an immunologist.

I, too, as well as Louis Tuft, have read, studied, and enjoyed Baer's book. Anything that people of the caliber of Rudolph Baer, Adolph Rostenberg, Marion Sulzberger, and the others who contributed chapters have to say must be taken seriously and considered with respect. However, they say some things which no allergist in his right mind can accept. For example, Rostenberg says: "My own observations are that in 20 years of studying this disease [atopic dermatitis] I have yet to see one case in which I was convinced that a given protein allergen played a causal role. There is much additional evidence which, to save time, I shall not cite, that removal from or de-sensitization to the suspected allergen does not affect the course of the disease."

These are astonishing statements, indeed, and contrary to the experience of most of those who deal with atopic dermatitis. All allergists, at any rate, many times have seen atopic dermatitis produced or worsened by foods or environmental allergens to which there is specific hypersensitivity. This seems to them as certain as the fact that pyogenic infection causes a boil. Furthermore, Tuft and his associates* have proved it experimentally beyond doubt. There can be no question, however, as Rostenberg has said, that many times "exposure to the suspected foods and other allergens does not cause a flare up." With this all are agreed, and there are good reasons for it which need not be discussed here. Rostenberg's statement applies often to many adults with atopic dermatitis. The situation is analogous to that of some patients with asthma of long-standing. No matter what they eat, no matter what they breathe, no matter what they do, no matter where they are, still they wheeze. The bronchial tubes have been habituated to wheezing for so long that they cannot act in any other way. Likewise, in many adults and in some older children who have atopic dermatitis a similar irreversible situation in the skin may develop. The trouble has gone far beyond the relative simplicity of an antigen-antibody reaction, and the usual methods of immunologic treatment may do no good whatever. There is too much here that nobody now understands.

I would like to see a young, enthusiastic, and brilliant man, preferably with no wife or children to complicate his existence, but with a thorough immunologic, dermatologic, and allergic training, liberally subsidized for a period of several years so that his entire energies and professional interests might be consumed by fundamental research on atopic dermatitis. Let him have a little ward of ten beds in a big general hospital; let him have a special outpatient clinic devoted to nothing but atopic dermatitis; let him have a well-equipped laboratory, plus a technician; let him devote all his energies to atopic dermatitis. The trouble with most of us is that we do private practice in order to eat and to keep a roof over our heads, and because many of us like it; this is our main business. We do not have a single-minded, blazing devotion to investigation. What we do is pretty good; it is not good enough. Atopic

*Tuft, Louis, Tuft, Harold S., and Heck, V. Muriel: Atopic Dermatitis, an Experimental Clinical Study of the Rôle of Inhalant Allergens, J. Allergy 21: 181, 1950.

dermatitis is one of the most complicated and obscure situations in all medicine; it is very common and it causes a great amount of suffering. It needs zealous and concentrated research of the same type that is now applied to cancer.

I always like to quote my favorite passage of medical literature, from Claude Bernard's *Introduction to Experimental Medicine.* It applies well to controversies between dermatologists and allergists.

"It happens quite naturally that men who believe too firmly in their theories do not believe enough in the theories of others. We must disregard our own opinion quite as much as the opinion of others when faced with the decisions of experience. When two physiologists or doctors quarrel,* each to maintain his own ideas or theories, in the midst of contradictory arguments, only one thing is absolutely certain, that both theories are insufficient and neither of them corresponds to the truth . . . we really know very little, and we are all fallible when facing the immense difficulties presented by investigation of natural phenomena."

Lewis Webb Hill.

*The word "quarrel" is not good here. As far as I know, Tuft, Rostenberg, Baer and Hill are very good friends; "politely disagree" would be better.

Correspondence

To the Editor:

Dr. Louis Tuft's Letter to the Editor in the May, 1956, issue of the JOURNAL OF ALLERGY suggests to me that the small book on *Atopic Dermatitis* (New York University Press), of which I am the editor, is fulfilling its purpose. Apparently, the point is clearly set forth that atopic dermatitis is *not just* an allergic disease.

Dr. Tuft states that Sulzberger (who, incidentally, contributed a chapter to the book, *Atopic Dermatitis*) and Coca, in 1934, took this dermatosis out of the dermatologic scrapheap of "eczemas" by proving its allergic basis and designating it "atopic dermatitis." I, as well as the other contributors to *Atopic Dermatitis*, mean, by the word *atopic*, having a peculiar hereditary tendency which expresses itself in certain stigmata in patients with atopic dermatitis, allergic asthma, allergic rhinitis, etc. There are, however, many other stigmata found in atopic dermatitis patients which quite apparently are neither a part of the atopic tendency nor, as far as one can tell, of any type of antigen-antibody interaction. White dermographism and cataract formation are pertinent examples. While admitting that the contributors to *Atopic Dermatitis* recognize the atopic hereditary background which very often is present in this dermatosis, Dr. Tuft seems to be concerned about the fact that they do not consider solely the allergic factor and, even worse, that they do not even necessarily consider it the single major etiological factor. He goes on to state that the doubts regarding the allergic etiology of atopic dermatitis as presented in the book threaten to turn back the clock of progress by several decades, and worries about the book's purpose and its possible influence upon those who are called upon to treat patients with this disease.

In the book, we were concerned solely with the presentation of the very considerable present-day knowledge of atopic dermatitis, including the many apparently nonallergic stigmata often found in patients with this disease. I feel that abandoning a one-sided, even though time-honored, approach to the atopic dermatitis problem and refusing to close one's eyes to the newer knowledge hardly can be termed turning back the clock!

Dr. Tuft further states that there would be no more justification for a dermatologist to treat a patient with atopic dermatitis without the aid of an allergist than there would be for an allergist to treat a case of pemphigus. Arguments as to which specialists are more capable of managing a given disease are, in my opinion, not part of the issue involved and are quite fruitless. Nevertheless, it must be stated, in all fairness. that while certain physicians may believe that the immunologic management of the disease is often successful, the majority have found this approach alone eminently unsatisfactory. Moreover, I must point out that the relationship of atopic dermatitis to asthma, hay fever, and gastrointestinal disturbances was recognized by dermatologists long before the word "allergy" came into existence in 1906 (see, for example, Besnier, 1892!) and that they were fully aware of the role played by allergic factors in some cases of atopic dermatitis even before Sulzberger and Coca coined the term "atopic dermatitis" (see, for example, Rost and Marchionini, 1932). Anyone who takes the time to study the literature on atopic dermatitis will find not only that much of the original immunologic work dealing with atopic dermatitis was done by dermatologists, but also that practically all the recent advances in the knowledge about this disease have been made by dermatologists. Examples of these advances are: disturbances in sweating, disturbances in vascular physiology including skin temperature regulation, and disturbances in response to stress, to mention only a few.

Dr. Tuft is mistaken if he thinks that dermatologists are ready to abandon the name "atopic dermatitis." The very book he criticizes bears the title *Atopic Dermatitis*, and on the program of the forthcoming International Dermatological Congress in Stockholm in 1957 is listed a major symposium on "Atopic Dermatitis (Prurigo Besnier, Neurodermatitis)."

The wealth of diverse and stimulating information now available about this disease may, quite naturally, be confusing to some. To me, however, this is not a discouarging sign but, rather, one of a broadening view of the entire atopic dermatitis problem, and a herald of further advances toward understanding its basic mechanisms and improving its management.

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Announcements

Hawaiian Session of American Academy of Allergy

The American Academy of Allergy will conduct a Hawaiian Session in connection with the 1957 annual meeting. A complete and comprehensive sight-seeing schedule has been arranged to permit visitors to view the islands of Oahu, Hawaii, and Maui. A special *luau* (Hawaiian feast) has been planned.

A scientific session will be held on Friday, Feb. 15, 1957, under the sponsorship of the Honolulu County Medical Society.

Transportation to and from Hawaii will be by United Air Lines chartered planes. Ship transportation can also be arranged to leave San Francisco on Feb. 9, 1957, and arrive in Honolulu on Feb. 13, 1957. Returning ships leave Honolulu on February 13 and arrive in Los Angeles on February 18, or leave Honolulu on February 25 and arrive in San Francisco on March 2.

The sight-seeing tours will cover the points of interest on the fascinating island of Oahu, including the Nuuanu Valley, the Buddhist Temple, the royal mausoleum, the Mormon Temple, and Pearl Harbor. A three-day interisland tour, visiting Maui and Hawaii, seeing lani and Moloki has been scheduled for Tuesday, February 12, through Thursday, February 14. This tour will include a visit to Rainbow Falls, Panaewa Forest, Hawaii National Park, Fern Tree Forest, and the crater of Kilauea.

The headquarters hotel in Hawaii will be the Princess Kaiulani at Waikiki Beach. This hotel has been selected because it is a first-class hotel. All transportation to and from Hawaii, between islands, and on sight-seeing tours has been arranged with first-class accommodations. Special rates are available for children.

Return to the United States is scheduled for Tuesday, Feb. 19, 1957, via United Air Lines.

Further information concerning reservations may be obtained by writing Mr. A. H. Luthmers, Assistant Executive Secretary, American Academy of Allergy, 208 E. Wisconsin Ave., Milwaukee 2, Wisconsin.

Dr. Freund Consultant to National Institute of Allergy and Infectious Diseases

Dr. Jules Freund, Chief of the Division of Applied Immunology, The Public Health Research Institute of the City of New York, has been appointed a consultant to the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, to assist in establishing its new Allergy-Immunology Program.

The experience and advice of Dr. Freund, leader in investigations in basic immunology and recognized throughout the world as outstanding in his field, will be utilized in the selection and evaluation of young investigators and in determining the methods of approach to pertinent problems in this area of research.

Meeting of the Third International Congress on Allergy of the International Association of Allergology

The Third International Congress on Allergy of the International Association of Allergology will meet in Paris, Oct. 26 to Nov. 1, 1958. Symposia and sectional meetings will include all phases of allergic diseases and immunology.

Address inquiries to Dr. Jose Quintero Fossas, Secretary, Paseo 313, Vedado, Havana, Cuba.

New Jersey Allergy Society

At the annual Atlantic City meeting of the New Jersey Allergy Society, the following officers were elected for the year of 1956-57:

President, E. J. Luippold, Boonton, New Jersey.
Vice-President, Harry Hershey, Jersey City, New Jersey.
Secretary, Frank H. Feldman, Newark, New Jersey.
Treasurer, Francis A. Pflum, Asbury Park, New Jersey.
To Executive Board, Solomon Aronoff, Jersey City, New Jersey.

California Society of Allergy

At its regular annual meeting in conjunction with the California Medical Association convention on May 1, 1956, in Los Angeles, the California Society of Allergy elected the following officers for 1956-57:

President, Ben C. Eisenberg, Huntington Park, California.
President-Elect, Willard S. Small, Pasadena, California.
Secretary-Treasurer, William J. Kerr, Jr., San Rafael, California.

Course in Allergy

The Faculty of Medicine of the University of Paris offers a course in allergic diseases under the direction of Prof. Pasteur Vallery-Radot, Oct. 15 to 25, 1956, at the Clinique Médicale propédeutique de l'Hôpital Broussais. The course will consist of theoretical lectures and practical demonstrations. Prof. Vallery-Radot is assisted by Drs. Halpern, Blamoutier, Gauthier-Villars, Sidi, Bernard-Dreyfus, Grabar, Holtzer, Wolfromm, Lhermitte, and Guillaumat. Enrollment is limited.

Applications should be addressed to la Clinique Médicale propédeutique de l'Hôpital Broussais, 96 rue Didot, Paris-XIV. Fee for the theoretical course, 5000 francs; for the complete course, 10,000 francs.